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NEWS 28 Oct 21 EVENTLINE has been reloaded
NEWS 29 Oct 24 BEILSTEIN adds new search fields
NEWS 30 Oct 24 Nutraceuticals International (NUTRACEUT) now available on STN
NEWS 31 Oct 25 MEDLINE SDI run of October 8, 2002
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NEWS 34 Dec 02 TIBKAT will be removed from STN
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NEWS 38 Dec 17 Adis Clinical Trials Insight now available on STN
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=> s TLR4
L1 1254 TLR4

=> s TLR2
L2 772 TLR2

=> s MyD88
L3 539 MYD88

=> s l1 (3a) (knockout or knock out or deficien? or transgen? or delet?)
L4 105 L1 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR DELET?)

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L5 50 DUP REM L4 (55 DUPLICATES REMOVED)

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L5 ANSWER 1 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2002:889458 CAPLUS
DN 137:381009
TI DNA sequence of human TLR4 gene and mutations associated with endotoxin hyporesponsiveness
IN Schwartz, David A.; Schutte, Brian C.; Lorenz, Eva
PA University of Iowa Research Foundation, USA
SO U.S. Pat. Appl. Publ., 56 pp., Cont.-in-part of Appl. No. PCT/0US00/15723.
CODEN: USXXCO
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI US 2002173001	A1	20021121	US 2001-10066	20011207
WO 2000077204	A1	20001221	WO 2000-US15723	20000608

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PRAI US 1999-329515 A2 19990610
WO 2000-US15723 A1 20000608
AB The invention provides variants of human gene TLR4 (encoding the toll-like receptor-4) which affect responsiveness to inhaled lipopolysaccharide (LPS). The studies show that common, co-segregating missense mutations (Asp299Gly and Thr399Ile) affecting the extracellular domain of the TLR4 receptor are assocd. with a blunted response to inhaled LPS in humans. Genetic evidence are provided to demonstrate common mutations in TLR4 are assocd. with differences in LPS responsiveness in humans. The invention provides methods to identify polymorphisms at the human TLR4 locus, as well as methods to identify individuals at risk of indications that increase their morbidity and mortality.

L5 ANSWER 2 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2003:8582 BIOSIS
DN PREV200300008582
TI Regions of the mouse CD14 molecule required for Toll-like receptor 2- and 4-mediated activation of NF-kappaB.
AU Muroi, Masashi; Ohnishi, Takahiro; Tanamoto, Ken-Ichi (1)
CS (1) Division of Microbiology, National Institute of Health Sciences, 1-18-1 Kamiyoga, Setagaya, Tokyo, 158-8501, Japan: tanamoto@nihs.go.jp Japan
SO Journal of Biological Chemistry, (November 1 2002) Vol. 277, No. 44, pp. 42372-42379. print.
ISSN: 0021-9258.
DT Article
LA English
AB Regions of mouse CD14 required for Toll-like receptor 2 (TLR2)- and TLR4-mediated activation of NF-kappaB were studied in transiently transfected 293 cells. Wild-type CD14 enhanced lipopolysaccharide (LPS)-induced NF-kappaB-dependent reporter activity in cells expressing ***TLR4*** /MD-2, and ***deletion*** of amino acid regions, 35-44, 144-153, 235-243, and 270-275 impaired the TLR4-mediated activation. Unlike human CD14, mouse CD14 truncated at amino acid 151 lost the activity. Deletion of amino acids 35-44 or 235-243 also abrogated TLR2-mediated activation of NF-kappaB, whereas mutants lacking 144-153 and 270-275 retained the activity. Deletion and alanine substitution experiments revealed that amino acids 151-153 and 273-275 were required for the ***TLR4*** -mediated activation. Both ***deletion*** mutants lacking amino acids 35-44 and 235-243 and alanine substitution mutants in regions 151-153 and 273-275 were expressed on the cell surface

and retained the ability to associate with TLR4. A cross-linking study with photoreactive LPS showed that the labeling intensities to CD14 mutants/TLR4/MD-2 were paralleled by the ability of CD14 mutants to increase TLR4-mediated activation. These results indicate that different regions of mouse CD14 are required for TLR4- and TLR2-mediated activation of NF-kappaB and suggest that amino acids 35-44, 151-153, 235-243, and 273-275 of mouse CD14 play an important role in LPS binding and its transfer to TLR4/MD-2.

L5 ANSWER 3 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:583920 BIOSIS
DN PREV200200583920
TI Involvement of toll-like receptor (TLR) 2 and TLR4 in cell activation by mannuronic acid polymers.
AU Flo, Trude H.; Ryan, Liv; Latz, Eicke; Takeuchi, Osamu; Monks, Brian G.; Lien, Egil; Halaas, Oyvind; Akira, Shizuo; Skjak-Braek, Gudmund; Golenbock, Douglas T.; Espevik, Terje (1)
CS (1) Institute of Cancer Research and Molecular Biology, Norwegian University of Science and Technology, 7489, Trondheim: terje.espevik@medisin.ntnu.no Norway
SO Journal of Biological Chemistry, (September 20, 2002) Vol. 277, No. 38, pp. 35489-35495. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB The alginate capsule produced by the human pathogen Pseudomonas aeruginosa
is composed mainly of mannuronic acid polymers (poly-M) that have immunostimulating properties. Poly-M shares with lipopolysaccharide the ability to stimulate cytokine production from human monocytes in a CD14-dependent manner. In the present study we examined the role of Toll-like receptor (TLR) 2 and TLR4 in responses to poly-M. Blocking antibodies to TLR2 and TLR4 partly inhibited tumor necrosis factor production induced by poly-M in human monocytes, and further inhibition was obtained by combining the antibodies. By transiently transfecting HEK293 cells, we found that membrane CD14 together with either TLR2 or TLR4/MD-2 could mediate activation by poly-M. Transfection of HEK293 cells with TLR2 and fluorescently labeled TLR4 followed by co-patching of TLR2 with an antibody revealed no association of these molecules on the plasma membrane. However, macrophages from the Tlr4 mutant C3H/HeJ mice and ***TLR4*** ***knockout*** mice were completely non-responsive to poly-M, whereas the tumor necrosis factor release from TLR2 knockout macrophages was half of that seen with wild type cells. Taken together the results suggest that both TLR2 and TLR4 are involved in cell activation by poly-M and that TLR4 may be required in primary murine macrophages.

L5 ANSWER 4 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 2002:382997 BIOSIS
DN PREV200200382997
TI Cutting edge: MyD88 is required for resistance to Toxoplasma gondii infection and regulates parasite-induced IL-12 production by dendritic cells.
AU Scanga, Charles A. (1); Aliberti, Julio; Jankovic, Dragana; Tilloy, Florence; Bennouna, Soumaya; Denkers, Eric Y.; Medzhitov, Ruslan; Sher, Alan
CS (1) Immunobiology Section, Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, 50 South Drive, Building 50, Room 6148, Bethesda, MD, 20892: cscanga@niaid.nih.gov USA
SO Journal of Immunology, (June 15, 2002) Vol. 168, No. 12, pp. 5997-6001. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Host resistance to the intracellular protozoan Toxoplasma gondii is highly dependent on early IL-12 production by APC. We demonstrate here that both host resistance and T. gondii-induced IL-12 production are dramatically reduced in mice lacking the adaptor molecule MyD88, an important signaling element used by Toll-like receptor (TLR) family members. Infection of MyD88-deficient mice with T. gondii resulted in uncontrolled parasite replication and greatly reduced plasma IL-12 levels. Defective IL-12 responses to T. gondii Ags (soluble tachyzoite Ag (STAg)) were observed in MyD88-/- peritoneal macrophages, neutrophils, and splenic dendritic cells (DC). In contrast, DC from TLR2- or ***TLR4*** - ***deficient*** animals developed normal IL-12 responses to STAg. In vivo treatment with pertussis toxin abolished the residual IL-12 response displayed by STAg-stimulated DC from MyD88-/- mice. Taken together, these data suggest that the induction of IL-12 by T. gondii depends on a unique mechanism involving both MyD88 and G protein-coupled signaling pathways.

L5 ANSWER 5 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 2002:495637 BIOSIS
DN PREV200200495637
TI Toll-like receptor 4 (***TLR4***)- ***deficient*** murine macrophage cell line as an in vitro assay system to show TLR4-independent signaling of Bacteroides fragilis lipopolysaccharide.
AU Lorenz, Eva (1); Patel, Dhavalkumar D.; Hartung, Thomas; Schwartz, David A.
CS (1) Section of Molecular Medicine and Infectious Diseases, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157-1042: elorenz@wfubmc.edu USA
SO Infection and Immunity, (September, 2002) Vol. 70, No. 9, pp. 4892-4896. print.
ISSN: 0019-9567.
DT Article
LA English
AB Bacterial lipopolysaccharides (LPS) activate cells of innate immunity, such as macrophages, by stimulating signaling through toll-like receptor 4 (TLR4). We and others have hypothesized that LPS derived from different bacterial species may function through TLR4-independent mechanisms. To test this hypothesis, we have generated using a nonviral transformation procedure a bone marrow-derived macrophage cell line called 10ScNCr/23 from mouse strain C57BL/10ScNCr. This mouse strain has a ***deletion*** of the ***TLR4*** locus, causing the mouse strain to be nonresponsive to stimulation by LPS from Escherichia coli while responding normally to other bacterial substrates, such as lipoteichoic acid (LTA) from Staphylococcus aureus, which signal TLR4 independently. Stimulation with LTA induces five- and sixfold increases in 10ScNCr/23 cell line tumor necrosis factor alpha and macrophage inflammatory protein-2 (MIP-2) secretion, but no increases in either cytokine were found when cells were stimulated with E. coli LPS. Bacteroides fragilis-derived LPS, however, can effectively stimulate MIP-2 expression in the absence of functional TLR4 in the 10ScNCr/23 cell line. This gives rise to the notion that LPS from some bacterial species will utilize alternative receptors to stimulate the innate immune response.

L5 ANSWER 6 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2002:561077 BIOSIS
DN PREV200200561077
TI Cellular activation, phagocytosis, and bactericidal activity against group B streptococcus involve parallel myeloid differentiation factor 88-dependent and independent signaling pathways.
AU Henneke, Philipp; Takeuchi, Osamu; Malley, Richard; Lien, Egil; Ingalls, Robin R.; Freeman, Mason W.; Mayadas, Tanya; Nizet, Victor; Akira, Shizuo; Kasper, Dennis L.; Golenbock, Douglas T. (1)
CS (1) Department of Medicine, Medical School, University of Massachusetts, 364 Plantation Street, Lazare Research Building, Room 309, Worcester, MA, 01605: douglas.golenbock@umassmed.edu USA
SO Journal of Immunology, (October 1, 2002) Vol. 169, No. 7, pp. 3970-3977. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Group B streptococci (GBS) vigorously activate inflammatory responses. We reported previously that a secreted GBS "factor" activates phagocytes via Toll-like receptor (TLR)2 and TLR6, but that GBS cell walls activate cells independently of these receptors. We hypothesized that the phagocytic immune functions in response to GBS, such as inflammation, uptake, and elimination of bacteria, occur through a coordinated engagement of TLRs, along with the coreceptors CD14 and CD11b/CD18. Using various knockout mice we show that GBS-induced activation of p38 and NF-kappaB depends upon
the expression of the cytoplasmic TLR adapter protein, myeloid differentiation factor 88 (MyD88), but not TLR2 and/or ***TLR4*** . Macrophages with ***deletions*** of CD14 and complement receptor 3 had a normal cytokine response to whole bacteria, although the response to GBS factor was abrogated in CD14-null cells. The intracellular formation of bactericidal oxygen species proved to be MyD88 dependent; however, uptake of GBS, a prerequisite for intracellular killing by O2 radicals, occurred independently of MyD88. While deletion of complement receptor 3 greatly diminished the uptake of opsonized GBS, it did not affect the formation of bactericidal O2 radicals or inflammatory signaling intermediates. We conclude that the inflammatory, bactericidal, and phagocytic responses to GBS occur via parallel but independent processes.

L5 ANSWER 7 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002284166 EMBASE
TI Lipopolysaccharide-induced leukocyte-endothelial cell interactions: A role for CD14 versus toll-like receptor 4 within microvessels.
AU Andonegui G.; Goyert S.M.; Kubes P.
CS Dr. P. Kubes, Department of Physiology, University of Calgary, 3330 Hospital Drive NW, Calgary, Alta. T2N 4N1, Canada. pkubes@ucalgary.ca
SO Journal of Immunology, (15 Aug 2002) 169/4 (2111-2119).
Refs: 57
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB The objective of this study was to systematically assess leukocyte-endothelial cell interactions in vivo in response to LPS in CD14-deficient (CD14(-/-)) and Toll-like receptor 4- ***deficient*** (***TLR4*** (d); C3H/HeJ) mice. Local injection of LPS (0.05 .mu.g/kg) into muscle at a concentration that did not cause systemic effects produced a significant reduction in the speed with which leukocytes roll and a substantial increase in leukocyte adhesion and emigration 4 h

postinjection. There was no response to LPS in the muscle microvasculature of CD14(-/-) mice or TLR4(d) animals. Systemic LPS induced leukopenia and significant sequestration of neutrophils in lungs in wild-type mice but not in CD14(-/-) or TLR4(d) mice. P-selectin expression was examined in numerous mouse organs using a dual radiolabeling mAb technique. The results revealed a 20- to 50-fold increase in P-selectin expression in response to LPS in all wild-type tissues examined but no response in any TLR4(d) tissues. Surprisingly, there was consistently a partial, significant increase in P-selectin expression in numerous microvasculatures including skin and pancreas, but no increase in P-selectin was detected in lung, muscle, and other organs in CD14(-/-) mice in response to LPS. Next, the skin and muscle microcirculation were visualized using intravital microscopy after systemic LPS treatment, and the results confirmed a CD14-independent mechanism of leukocyte sequestration in skin but not muscle. In summary, our results suggest that the LPS-induced leukocyte sequestration to some tissues is entirely dependent on both CD14 and TLR4 but there are CD14-independent, TLR4-dependent endothelial cell responses in some microvascular beds.

L5 ANSWER 8 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 2002:329612 BIOSIS
DN PREV200200329612
TI Differential responses of mast cell Toll-like receptors 2 and 4 in allergy and innate immunity.
AU Supajatura, Volaluck; Ushio, Hiroko (1); Nakao, Atsuhito; Akira, Shizuo; Okumura, Ko; Ra, Chisei; Ogawa, Hideoki
CS (1) Atopy (Allergy) Research Center, Juntendo University School of Medicine, 2-1-1 Hongo, Bunkyo-ku, Tokyo, 113-8421: hushio@med.juntendo.ac.jp Japan
SO Journal of Clinical Investigation, (May, 2002) Vol. 109, No. 10, pp. 1351-1359. http://www.jci.org/. print.
ISSN: 0021-9738.
DT Article
LA English
AB Toll-like receptor 2 (TLR2) and TLR4 play important roles in the early innate immune response to microbial challenge. To clarify the functional roles of TLRs 2 and 4 in mast cells, we examined bone marrow-derived mast cells (BMMCs) from TLR2 or TLR4 gene-targeted mice. Peptidoglycan (PGN) from Staphylococcus aureus stimulated mast cells in a TLR2-dependent manner to produce TNF-alpha, IL-4, IL-5, IL-6, and IL-13, but not IL-1beta. In contrast, LPS from Escherichia coli stimulated mast cells in a TLR4-dependent manner to produce TNF-alpha, IL-1beta, IL-6, and IL-13, but not IL-4 nor IL-5. Furthermore, TLR2- but not TLR4-dependent mast cell stimulation resulted in mast cell degranulation and Ca2+ mobilization. In a mast cell-dependent model of acute sepsis, ***TLR4*** ***deficiency*** of BMMCs in mice resulted in significantly higher mortality because of defective neutrophil recruitment and production of proinflammatory cytokines in the peritoneal cavity. Intradermal injection of PGN led to increased vasodilatation and inflammation through TLR2-dependent activation of mast cells in the skin. Taken together, these results suggest that direct activation of mast cells via TLR2 or TLR4 by respective microligands contributes to innate and allergic immune responses.

L5 ANSWER 9 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2002:839869 CAPLUS
TI Cell activation by Porphyromonas gingivalis lipid A molecule through Toll-like receptor 4- and myeloid differentiation factor 88-dependent signaling pathway
AU Ogawa, Tomohiko; Asai, Yasuyuki; Hashimoto, Masahito; Takeuchi, Osamu; Kurita, Tomoko; Yoshikai, Yasunobu; Miyake, Kensuke; Akira, Shizuo
CS Department of Oral Microbiology, Asahi University School of Dentistry, Motosu-Gun, Gifu, 501-0296, Japan
SO International Immunology (2002), 14(11), 1325-1332
CODEN: INIMEN; ISSN: 0953-8178
PB Oxford University Press
DT Journal
LA English
AB P. gingivalis lipopolysaccharide (LPS) and its bioactive center, lipid A, are known to exhibit very low endotoxic activities and activate LPS-hyporesponsive C3H/HeJ mice that have a point mutation in the cytoplasmic portion of Toll-like receptor (TLR) 4, in contrast to classical enterobacterial LPS and their lipid A. Here, the authors attempted to det. which TLR mediates the response to lipid A from P. gingivalis strain 381. P. gingivalis LPS and its natural lipid A fraction induced NF-.kappa.B activation primarily in Ba/F3 cells expressing mouse TLR2 (Ba/mTLR2), rather than in those expressing mouse TLR4 and its accessory protein MD2 (Ba/mTLR4/mMD2). Further purifn. of the natural lipid A fraction resulted in a decrease of NF-.kappa.B activation in Ba/mTLR2, although not in Ba/mTLR4/mMD2. The synthetic counterpart of P. gingivalis strain 381-lipid A (compd. PG-381) also elicited NF-.kappa.B activation in Ba/mTLR4/mMD2, but not Ba/mTLR2. Furthermore, P. gingivalis purified natural lipid A and compd. PG-381 lacked the ability to activate gingival fibroblasts from C3H/HeJ, ***TLR4*** ***knockout*** (KO), and myeloid differentiation factor 88 (MyD88) KO mice. These findings demonstrate that the P. gingivalis lipid A mol. induces cell activation via a TLR4/MD2-MyD88-dependent pathway, and suggest the possibility that unknown bacterial components in P. gingivalis LPS and its lipid A may induce cell activation via TLR2.
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

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L5 ANSWER 10 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 2002:612137 BIOSIS
DN PREV200200612137
TI Differential involvement of IFN-beta in Toll-like receptor-stimulated dendritic cell activation.
AU Hoshino, Katsuaki; Kaisho, Tsuneyasu; Iwabe, Tomio; Takeuchi, Osamu; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO International Immunology, (October, 2002) Vol. 14, No. 10, pp. 1225-1231. http://www.intimm.oupjournals.org. print.
ISSN: 0953-8178.
DT Article; Conference
LA English
AB Toll-like receptor (TLR) can activate dendritic cells (DC) through common signaling pathways requiring a cytoplasmic adapter, MyD88. However, the signaling is differentially regulated among TLR family members. ***TLR4*** can activate MyD88- ***deficient*** bone marrow-derived DC (BMDC), and lead to induction of IFN-inducible genes and up-regulation of co-stimulatory molecules such as CD40, implying that the MyD88-independent signaling pathway functions downstream of TLR4. Because these effects can also be induced by type I IFN, we have analyzed whether type I IFN is involved in TLR4-induced responses. In response to lipopolysaccharide (LPS), IFN-beta gene expression was augmented in both wild-type and MyD88-deficient BMDC. Expression of all IFN-inducible genes except immune-responsive gene 1 (IRG1) was abolished and CD40 up-regulation was decreased in LPS-stimulated BMDC lacking either IFN-alpha/beta receptor (IFN-alpha/betaR) or signal transducer and activator of transcription 1 (STAT-1). Similar to the LPS response, TLR9 signaling can also induce expression of IFN-beta and IFN-inducible genes, and up-regulation of CD40. However, all these effects were MyD88 dependent. Thus, in TLR4 signaling, IFN-beta expression can be induced either by the MyD88-dependent or -independent pathway, whereas, in TLR9 signaling, it is dependent on MyD88. In CpG DNA-stimulated DC, expression of IFN-inducible genes except IRG1 was dependent on type I IFN signaling as in LPS-stimulated DC. However, in contrast to TLR4 signaling, TLR9 signaling requires type I IFN signaling for CD40 up-regulation. Taken together, this study demonstrates differential involvement of type I IFN in TLR4- and TLR9-induced effects on DC.

L5 ANSWER 11 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 2003:9123 BIOSIS
DN PREV200300009123
TI Involvement of MyD88 in host defense and the down-regulation of anti-heat shock protein 70 autoantibody formation by MyD88 in Toxoplasma gondii-infected mice.
AU Chen, M.; Aosai, F.; Norose, K.; Mun, H.-S.; Takeuchi, O.; Akira, S.; Yano, A. (1)
CS (1) Department of Infection and Host Defense, Graduate School of Medicine, Chiba University, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8670, Japan: yano@med.m.chiba-u.ac.jp Japan
SO Journal of Parasitology, (October 2002, 2002) Vol. 88, No. 5, pp. 1017-1019. print.
ISSN: 0022-3395.
DT Article
LA English
AB This study investigated the influence of TLR (toll-like receptor)4, TLR2, and MyD88 in Toxoplasma gondii-infected wild-type (WT) mice and ***TLR4*** -, TLR2-, and MyD88- ***deficient*** mice. Ninety-five percent of MyD88-deficient mice died 10-16 days after intraperitoneal infection with 100 cysts of T. gondii Fukaya strain, whereas 95-100% of ***TLR4*** - and TLR2- ***deficient*** mice and WT C57BL/6 (B6) mice survived for more than 7 wk after T. gondii infection. The distribution of T. gondii in various organs of ***TLR4*** -, TLR2-, and MyD88- ***deficient*** mice and WT B6 mice was assessed 2 wk after T. gondii intraperitoneal infection using quantitative competitive polymerase chain reaction. In MyD88-deficient mice, high levels of T. gondii load were observed in the brain, tongue, heart, lungs, spleen, liver, mesenteric lymph node, and kidneys after infection. The T. gondii load was significantly increased in the lungs in both ***TLR4*** - and TLR2- ***deficient*** mice compared with WT B6 mice. High levels of anti-mouse heat shock protein (mHSP)70 autoantibody and anti-T. gondii HSP70 antibody production were detected in the sera from MyD88-deficient mice.

L5 ANSWER 12 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 2002:589906 BIOSIS
DN PREV200200589906
TI Toll-like receptor 4 mediates innate immune responses to Haemophilus influenzae infection in mouse lung.
AU Wang, Xiaorong; Moser, Christian; Louboutin, Jean-Pierre; Lysenko, Elena S.; Weiner, Daniel J.; Weiser, Jeffrey N.; Wilson, James M. (1)
CS (1) Wistar Institute, University of Pennsylvania, 3601 Spruce Street, 204, Philadelphia, PA, 19104: wilsonjm@mail.med.upenn.edu USA
SO Journal of Immunology, (January 15, 2002) Vol. 168, No. 2, pp. 810-815.

http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Toll-like receptors (TLRs) have been implicated in the regulation of host responses to microbial Ags. This study characterizes the role of TLR4 in the innate immune response to intrapulmonary administration of Haemophilus influenzae in the mouse. Two different strains of mice efficiently cleared aerosolized H. influenzae concurrent with a brisk elaboration of IL-1beta, IL-6, TNF-alpha, macrophage-inflammatory protein (MIP)-1alpha, and MIP-2 in bronchoalveolar lavage and a corresponding mobilization of intrapulmonary neutrophils. Congenic strains of mice ***deficient*** in ***TLR4*** demonstrated a substantial delay in clearance of H. influenzae with diminished IL-1beta, IL-6, TNF-alpha, MIP-1alpha, and MIP-2 in bronchoalveolar lavage and a notable absence of intrapulmonary neutrophils. In TLR4-expressing animals, but not ***TLR4*** - ***deficient*** animals, TNF-alpha and MIP-1alpha expression was up-regulated in epithelial cells of the conducting airway in response to H. influenzae which was preceded by an apparent activation of the NF-kappaB pathway in these cells based on the findings of decreased overall IkappaB and an increase in its phosphorylated form. This study demonstrates a critical role of TLR4 in mediating an effective innate immune response to H. influenzae in the lung. This suggests that the airway epithelia might contribute to sensing of H. influenzae infection and signaling the innate immune response.

L5 ANSWER 13 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 2002:589879 BIOSIS
DN PREV200200589879
TI The receptor for heat shock protein 60 on macrophages is saturable, specific, and distinct from receptors for other heat shock proteins.
AU Habich, Christiane (1); Baumgart, Karina; Kolb, Hubert; Burkart, Volker
CS (1) Clinical Department, German Diabetes Research Institute, Auf'm Hennekamp 65, D-40225, Duesseldorf: christiane.habich@ddfi.uni-duesseldorf.de Germany
SO Journal of Immunology, (January 15, 2002) Vol. 168, No. 2, pp. 569-576. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Previous studies have shown that human heat shock protein (hsp) 60 elicits a strong proinflammatory response in cells of the innate immune system with CD14, Toll-like receptor (TLR) 2, and TLR4 as mediators of signaling, but probably not of binding. In the present study, we directly demonstrate binding of hsp60 to the macrophage surface and find the binding receptor for hsp60 different from the previously described common receptor for several other heat shock proteins, including hsp70, hsp90, and gp96. Fluorescence-labeled human hsp60 bound to cell surfaces of the murine macrophage lines J774 A.1 and RAW264.7 and to mouse bone marrow-derived macrophages. By flow cytometry, we could demonstrate for the first time that hsp60 binding to macrophages occurred at submicromolar concentrations, is saturable, and can be competed by unlabeled hsp60, but not by unrelated proteins, thus confirming the classic characteristics of specific ligand-receptor interactions. Binding of hsp60 at 4degreeC was followed by endocytosis at 37degreeC. Hsp60 binding to macrophages could not be competed by excess hsp70, hsp90, or gp96, all of which share the alpha2-macroglobulin receptor as binding site. Hsp60 binding occurred in the absence of surface TLR4. However, no cytokine response was induced by hsp60 in ***TLR4*** - ***deficient*** macrophages. We conclude that hsp60 binds to a stereo-specific receptor on macrophages, and that different surface molecules are engaged in binding and signal transduction. Furthermore, the binding site for hsp60 is separate from the common receptor for hsp70, hsp90, and gp96, which suggests an independent role of hsp60 as danger Ag and in immunoregulation.

L5 ANSWER 14 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
11
AN 2003:367 BIOSIS
DN PREV200300000367
TI The adaptor molecule TIRAP provides signalling specificity for Toll-like receptors.
AU Horng, Tiffany; Barton, Gregory M.; Flavell, Richard A.; Medzhitov, Ruslan (1)
CS (1) Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT, 06520, USA: ruslan.medzhitov@yale.edu USA
SO Nature (London), (21 November 2002) Vol. 420, No. 6913, pp. 329-333. print.
ISSN: 0028-0836.
DT Article; Letter
LA English
AB Mammalian Toll-like receptors (TLRs) function as sensors of infection and induce the activation of innate and adaptive immune responses. Upon recognizing conserved pathogen-associated molecular products, TLRs activate host defence responses through their intracellular signalling domain, the Toll/interleukin-1 receptor (TIR) domain, and the downstream adaptor protein MyD88 (refs 1-3). Although members of the TLR and the interleukin-1 (IL-1) receptor families all signal through MyD88, the signalling pathways induced by individual receptors differ. TIRAP, an adaptor protein in the TLR signalling pathway, has been identified and shown to function downstream of TLR4 (refs 4, 5). Here we report the generation of mice deficient in the Tirap gene. TIRAP-deficient mice respond normally to the TLR5, TLR7 and TLR9 ligands, as well as to IL-1 and IL-18, but have defects in cytokine production and in activation of the nuclear factor NF-kappaB and mitogen-activated protein kinases in response to lipopolysaccharide, a ligand for ***TLR4*** . In addition, TIRAP- ***deficient*** mice are also impaired in their responses to ligands for TLR2, TLR1 and TLR6. Thus, TIRAP is differentially involved in signalling by members of the TLR family and may account for specificity in the downstream signalling of individual TLRs.

L5 ANSWER 15 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:353628 BIOSIS
DN PREV200200353628
TI Roles of toll-like receptors in immunity against mycobacterial infection.
AU Heldwein, Kurt A. (1); Andresen, Tonje K. (1); Vogel, Stefanie N.; Fenton, Matthew J. (1)
CS (1) Pulmonary Center, Boston University School of Medicine, 80 E. Concord St., Boston, MA, 02118-2394 USA
SO FASEB Journal, (March 20, 2002) Vol. 16, No. 4, pp. A287. http://www.fasebj.org/. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology New Orleans, Louisiana, USA April 20-24, 2002
ISSN: 0892-6638.
DT Conference
LA English
AB Toll-like receptor (TLR) proteins are pattern recognition receptors that mediate cellular activation by a wide variety of bacterial products. We previously showed that live M. tuberculosis (Mtb) bacteria activate macrophages via both TLR2 and TLR4. We also found that these TLR proteins mediate the induction of TNF secretion by Mtb-stimulated macrophages. In contrast, nitric oxide (NO) production was not dependent on TLR signaling. This conclusion is based on the observation that Mtb-stimulated macrophages from MyD88-/- mice (i.e. mice that cannot signal via TLR proteins) released normal levels of NO, but did not secrete TNF. We subsequently sought to determine whether TLR2 and TLR4 participate in the control of mycobacterial infection in vivo, and whether these TLR proteins differentially mediate host responses. Using ***TLR4*** - ***deficient*** C3H/HeJ mice, we found that infection with live mycobacteria resulted in enhanced bacterial growth in vivo compared with normal C3H/OuJ mice. Furthermore, serum levels of IL-12p70 and gamma interferon were markedly lower in the infected C3H/HeJ mice compared with infected controls. Production of IL-12 and gamma interferon by antigen-primed splenic T cells was also impaired in cells from C3H/HeJ mice, compared to controls. These studies indicate that TLR proteins participate in both the innate and cell-mediated immune response against mycobacterial infection.

L5 ANSWER 16 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2002:588215 CAPLUS
TI TLR4-MD2 signaling pathway induced by endotoxin
AU Li, Yongwang; Ma, Li; Mao, Baoling; Qian, Guisheng
CS Institute of Respiratory Disease, Xinqiao Hospital, the Third Military Medical University, Chungking, 400037, Peop. Rep. China
SO Zhongguo Yaolixue Tongbao (2002), 18(2), 121-125
CODEN: ZYTOE8; ISSN: 1001-1978
PB Anhui Yike Daxue Linchuan Yaoli Yanjiuso
DT Journal; General Review
LA Chinese
AB A review with 24 refs. on TLR4-MD2 (TLR4 = toll-like receptor-4) signaling pathway induced by endotoxin with subdivision headings: (1) survey on TLRs; (2) role of TLR4 and its accessory protein MD2 in signaling pathway; (3) basic compn. of lipopolysaccharide (LPS) signaling pathway mediated by TLR4-MD2; Biol. significance of ***TLR4*** -MD2 signaling pathway ***deficiency*** ; (5) expression and role of TLR4-MD2 in different tissues; and (6) conclusions.

L5 ANSWER 17 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2002:970457 CAPLUS
TI Toll-like receptor-4 is involved in eliciting an LPS-induced oxidative burst in neutrophils
AU Remer, Katharina A.; Brcic, Marija; Jungi, Thomas W.
CS Institute of Veterinary Virology, University of Berne, Laenggass-Strasse 122, Bern, CH-3012, Switz.
SO Immunology Letters (2002), 85(1), 75-80
CODEN: IMLED6; ISSN: 0165-2478
PB Elsevier Science Ireland Ltd.
DT Journal
LA English
AB The lipopolysaccharide (LPS) receptor complex of mononuclear phagocytes is composed of Toll-like receptor-4 (TLR4), MD-2 and CD14. Other phagocyte populations may express similar LPS receptors. The transmembrane glycoprotein TLR4 was shown to induce or upregulate a variety of gene products, which collectively are the mediators of an LPS effect. In this study, an involvement of TLR4 in mediation of an oxidative burst was detd. using murine peritoneal exsudate neutrophils and lucigenin-enhanced chemiluminescence (CL). The CL response was dependent on the LPS dose and the presence of serum, putatively a source of lipopolysaccharide-binding protein (LBP). In the absence of serum, a CL signal was elicited by 4 .mu.g/mL LPS in peritoneal exsudate cells (PEC) from TLR4-sufficient (C3H/HeN) but not ***TLR4*** ***deficient*** (C3H/HeJ) mice. The

signal obtained in PEC from TLR4-sufficient mice was completely abrogated by superoxide dismutase (SOD), which indicated that the response depended on the formation of superoxide anion, and was also seen in purified neutrophils but not purified macrophages (M.phi.). In the presence of serum, lower LPS concns. (e.g. 40 ng/mL) elicited a strong CL response in PEC from TLR4-sufficient, and a weak signal in cells from TLR-4-deficient mice. This suggests that TLR4 engagement is involved in promoting an oxidative burst in murine neutrophils.

L5 ANSWER 18 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 2001:527373 BIOSIS
DN PREV200100527373
TI Involvement of Toll-like receptor 4 in innate immunity to respiratory syncytial virus.
AU Haynes, Lia M.; Moore, Deborah D.; Kurt-Jones, Evelyn A.; Finberg, Robert W.; Anderson, Larry J.; Tripp, Ralph A. (1)
CS (1) Division of Viral and Rickettsial Diseases, Respiratory Enteric Virology Branch, National Center for Infectious Diseases, 1600 Clifton Rd. NE, Mailstop G-09, Atlanta, GA, 30333: rgt3@cdc.gov USA
SO Journal of Virology, (November, 2001) Vol. 75, No. 22, pp. 10730-10737. print.
ISSN: 0022-538X.
DT Article
LA English
SL English
AB The mammalian Toll-like receptor 4, TLR4, is an important component in the innate immune response to gram-negative bacterial infection. The role of TLR4 in antiviral immunity has been largely unexplored. In this study, the in vivo immune responses to respiratory syncytial virus (RSV) and influenza virus infection were examined in ***TLR4*** -***deficient*** (C57BL/10ScNCr) and ***TLR4*** -expressing (C57BL/10Sn) mice. ***TLR4*** - ***deficient*** mice challenged with RSV, but not influenza virus, exhibited impaired natural killer (NK) cell and CD14+ cell pulmonary trafficking, deficient NK cell function, impaired interleukin-12 expression, and impaired virus clearance compared to mice expressing TLR4. These findings suggest that Toll signaling pathways have an important role in innate immunity to RSV.

L5 ANSWER 19 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2001:867389 CAPLUS
DN 136:132685
TI Differences in innate defense mechanisms in endotoxemia and polymicrobial septic peritonitis
AU Echtenacher, Bernd; Freudenberg, Marina A.; Jack, Robert S.; Mannel, Daniela N.
CS Max-Planck-Institute for Immunobiology, Freiburg, Germany
SO Infection and Immunity (2001), 69(12), 7271-7276
CODEN: INFIBR; ISSN: 0019-9567
PB American Society for Microbiology
DT Journal
LA English
AB Loss, redn., or enhancement of the ability to respond to bacterial lipopolysaccharide (LPS) has no influence on survival of mice in a model of postoperative polymicrobial septic peritonitis induced by cecal ligation and puncture (CLP). This was demonstrated by using either mice with a defective Tlr4 gene, which encodes the crit. receptor mol. for LPS responses, or mice deficient for LPS binding protein (LBP) or mice sensitized to LPS by Propionibacterium acnes. Though interleukin-12 (IL-12) and gamma interferon (IFN-.gamma.) play an important role in the sensitivity to LPS as well as in the resistance to several infections, loss of these cytokine pathways does not affect survival after CLP. Thus, neutralization of neither endogenous IL-12 nor IFN-.gamma. altered mortality. In addn., IFN-.gamma. receptor-deficient mice demonstrated the same sensitivity to CLP as mice with a functional IFN-.gamma. receptor. However, administration of IFN-.gamma. at the time of operation or pretreatment of both IFN-.gamma.-sensitive and IFN-.gamma.-resistant mice with IL-12 significantly enhanced mortality. This indicates that in the present infection model activation of innate defense mechanisms is not dependent on LPS recognition and does not require endogenous IL-12 or IFN-.gamma. function. Indeed, exogenous application of these two mediators had deleterious effects.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 20 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001404625 EMBASE
TI Lipopolysaccharide stimulates the MyaD88-independent pathway and results in activation of IFN-regulatory factor 3 and the expression of a subset of lipopolysaccharide-inducible genes.
AU Kawai T.; Takeuchi O.; Fujita T.; Inoue J.-I.; Muhlradt P.F.; Sato S.; Hoshino K.; Akira S.
CS Dr. S. Akira, Department of Host Defense, Res. Inst. for Microbial Diseases, Osaka University, 3-1 Yamadaoka Suita, Osaka 565-0871, Japan. sakira@biken.osaka-u.ac.jp
SO Journal of Immunology, (15 Nov 2001) 167/10 (5887-5894).
Refs: 52
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Bacterial lipopolysaccharide (LPS) triggers innate immune responses through Toll-like receptor (TLR) 4, a member of the TLR family that participates in pathogen recognition. TLRs recruit a cytoplasmic protein, MyD88, upon pathogen recognition, mediating its function for immune responses. Two major pathways for LPS have been suggested in recent studies, which are referred to as MyD88-dependent and -independent pathways. We report in this study the characterization of the MyD88-independent pathway via ***TLR4*** . MyD88- ***deficient*** cells failed to produce inflammatory cytokines in response to LPS, whereas they responded to LPS by activating IFN-regulatory factor 3 as well as inducing the genes containing IFN-stimulated regulatory elements such as IP-10. In contrast, a lipopeptide that activates TLR2 had no ability to activate IFN-regulatory factor 3. The MyD88-independent pathway was also activated in cells lacking both MyD88 and TNFR-associated factor 6. Thus, TLR4 signaling is composed of at least two distinct pathways, a MyD88-dependent pathway that is critical to the induction of inflammatory cytokines and a MyD88/TNFR-associated factor 6-independent pathway that regulates induction of IP-10.

L5 ANSWER 21 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 13
AN 2001156260 EMBASE
TI Endotoxin-induced maturation of MyD88-deficient dendritic cells.
AU Kaisho T.; Takeuchi O.; Kawai T.; Hoshino K.; Akira S.
CS Dr. S. Akira, Department of Host Defense, Res. Inst. for Microbial Diseases, Osaka University, Yamadaoka 3-1, Osaka 565-0871, Japan. sakira@biken.osaka-u.ac.jp
SO Journal of Immunology, (1 May 2001) 166/9 (5688-5694).
Refs: 34
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB LPS, a major component of the cell wall of Gram-negative bacteria, can induce a variety of biological responses including cytokine production from macrophages, B cell proliferation, and endotoxin shock. All of them were completely abolished in MyD88deficient mice, indicating the essential role of MyD88 in LPS signaling. However, MyD88-deficient cells still show activation of NF-.kappa.B and mitogen-activated protein kinase cascades, although the biological significance of this activation is not clear. In this study, we have examined the effects of LPS on dendritic cells (DCs) from wild-type and several mutant mice. LPS-induced cytokine production from DCs was dependent on MyD88. However, LPS could induce functional maturation of MyD88-deficient DCs, including up-regulation of costimulatory molecules and enhancement of APC activity. MyD88-deficient DCs could not maturate in response to bacterial DNA, the ligand for Toll-like receptor (TLR)9, indicating that MyD88 is differentially required for TLR family signaling. MyD88-dependent and -independent pathways originate at the intracytoplasmic region of TLR4, because both cytokine induction and functional maturation were abolished in DCs from C3H/HeJ mice carrying the point mutation in the region. Finally, in vivo analysis revealed that MyD88-, but not ***TLR4*** -, ***deficient*** splenic CD11c(+) DCs could up-regulate their costimulatory molecule expression in response to LPS. Collectively, the present study provides the first evidence that the MyD88-independent pathway downstrem of TLR4 can lead to functional DC maturation, which is critical for a link between innate and adaptive immunity.

L5 ANSWER 22 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 14
AN 2001380481 EMBASE
TI Lipopolysaccharides from distinct pathogens induce different classes of immune responses in vivo.
AU Pulendran B.; Kumar P.; Cutler C.W.; Mohamadzadeh M.; Van Dyke T.; Banchereau J.
CS Dr. B. Pulendran, Aventis Pharmaceuticals, Route 202-206, Bridgewater, NJ 08807-0800, United States. BaliPulendran@aventis.com
SO Journal of Immunology, (1 Nov 2001) 167/9 (5067-5076).
Refs: 62
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB The adaptive immune system has evolved distinct responses against different pathogens, but the mechanism(s) by which a particular response is initiated is poorly understood. In this study, we investigated the type of Ag-specific CD4(+) Th and CD8(+) T cell responses elicited in vivo, in response to soluble OVA, coinjected with LPS from two different pathogens. We used Escherichia coli LPS, which signals through Toll-like receptor 4 (TLR4) and LPS from the oral pathogen Porphyromonas gingivalis, which does not appear to require TLR4 for signaling. Coinjections of E. coli LPS + OVA or P. gingivalis LPS + OVA induced similar clonal expansions of OVA-specific CD4(+) and CD8(+) T cells, but strikingly different cytokine profiles. E. coli LPS induced a Th1-like response with abundant IFN-.gamma., but little or no IL-4, IL-13, and IL-5. In contrast, P. gingivalis LPS induced Th and T cell responses characterized by

significant levels of IL-13, IL-5, and IL-10, but lower levels of IFN-.gamma.. Consistent with these results, E. coli LPS induced IL-12(p70) in the CD8.alpha.(+) dendritic cell (DC) subset, while P. gingivalis LPS did not. Both LPS, however, activated the two DC subsets to up-regulate costimulatory molecules and produce IL-6 and TNF-.alpha.. Interestingly, these LPS appeared to have differences in their ability to signal through TLR4; proliferation of splenocytes and cytokine secretion by splenocytes or DCs from ***TLR4*** - ***deficient*** C3H/HeJ mice were greatly impaired in response to E. coli LPS, but not P. gingivalis LPS. Therefore, LPS from different bacteria activate DC subsets to produce different cytokines, and induce distinct types of adaptive immunity in vivo.

L5 ANSWER 23 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 15
AN 2001107729 EMBASE
TI Differential effects of a Toll-like receptor antagonist on Mycobacterium tuberculosis-induced macrophage responses.
AU Means T.K.; Jones B.W.; Schromm A.B.; Shurtleff B.A.; Smith J.A.; Keane J.; Golenbock D.T.; Vogel S.N.; Fenton M.J.
CS Dr. M.J. Fenton, Pulmonary Center, Boston University School of Medicine, Boston, MA 02118-2394, United States. mfenton@bu.edu
SO Journal of Immunology, (15 Mar 2001) 166/6 (4074-4082).
Refs: 54
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB We previously showed that viable Mycobacterium tuberculosis (Mtb) bacilli contain distinct ligands that activate cells via the mammalian Toll-like receptor (TLR) proteins TLR2 and TLR4. We now demonstrate that expression of a dominant negative TLR2 or TLR4 proteins in RAW 264.7 macrophages partially blocked Mtb-induced NF-.kappa.B activation. Coexpression of both dominant negative proteins blocked virtually all Mtb-induced NF-.kappa.B activation. The role of the TLR4 coreceptor MD-2 was also examined. Unlike LPS, Mtb-induced macrophage activation was not augmented by overexpression of ectopic MD-2. Moreover, cells expressing an LPS-unresponsive MD-2 mutant responded normally to Mtb. We also observed that the lipid A-like antagonist E5531 specifically inhibited TLR4-dependent Mtb-induced cellular responses. E5531 could substantially block LPS- and Mtb-induced TNF-.alpha. production in both RAW 264.7 cells and primary human alveolar macrophages (AM.phi.). E5531 inhibited Mtb-induced AM.phi. apoptosis in vitro, an effect that was a consequence of the inhibition of TNF-.alpha. production by E5531. In contrast, E5531 did not inhibit Mtb-induced NO production in RAW 264.7 cells and AM.phi.. Mtb-stimulated peritoneal macrophages from TLR2- and ***TLR4*** - ***deficient*** animals produced similar amounts of NO compared with control animals, demonstrating that these TLR proteins are not required for Mtb-induced NO production. Lastly, we demonstrated that a dominant negative MyD88 mutant could block Mtb-induced activation of the TNF-.alpha. promoter, but not the inducible NO synthase promoter, in murine macrophages. Together, these data suggest that Mtb-induced TNF-.alpha. production is largely dependent on TLR signaling. In contrast, Mtb-induced NO production may be either TLR independent or mediated by TLR proteins in a MyD88-independent manner.

L5 ANSWER 24 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 16
AN 2001:302989 BIOSIS
DN PREV200100302989
TI Upregulation of toll-like receptor 2 gene expression in macrophage response to peptidoglycan and high concentration of lipopolysaccharide is involved in NF-kappaB activation.
AU Liu, Yan; Wang, Yin; Yamakuchi, Munekazu; Isowaki, Sumikazu; Nagata, Etsuro; Kanmura, Yuichi; Kitajima, Isao; Maruyama, Ikuro (1)
CS (1) Department of Laboratory and Molecular Medicine, Kagoshima University School of Medicine, 8-35-1 Sakuragaoka, Kagoshima City, 890-8520: rinken1@khosp2.kufm.kagoshima-u.ac.jp Japan
SO Infection and Immunity, (May, 2001) Vol. 69, No. 5, pp. 2788-2796. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB Toll-like receptors 2 and 4 (TLR2 and TLR4) have been found to transduce signals of peptidoglycan (PGN) and lipopolysaccharide (LPS), respectively, for NF-kappaB activation. However, little is known about the expression and regulation of the TLR2 gene in monocytes/macrophages in response to the two typical bacterial products. We show in the present study that both PGN and a high concentration of LPS increase TLR2 gene expression in macrophage-like cells, 1alpha,25-dihydroxyvitamin D3-differentiated human HL60 and mouse RAW264.7 cells, and human monocytes in a dose- and time-dependent manner. Actinomycin D and pyrrolidine dithiocarbamate inhibition of gene transcription and NF-kappaB activation, respectively, blocks LPS- and PGN-elevated TLR2 mRNA in monocytic cells. The LPS-induced increase in TLR2 mRNA in monocytic cells is abolished by polymyxin B pretreatment and is observed in peripheral blood mononuclear cells from pigs subjected to endotoxic shock. Further, high concentrations of LPS and synthetic lipid A increase TLR2 mRNA expression in peritoneal macrophages from both ***TLR4*** - ***deficient*** C3H/HeJ mice and normal C3H/HeN mice, a process that constitutes induction of TLR4-independent TLR2 expression. These findings demonstrate that TLR2 gene expression is upregulated in macrophage responses to PGN and to high concentrations of LPS in vitro and in vivo and correlates with NF-kappaB activation.

L5 ANSWER 25 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 17
AN 2001:429207 BIOSIS
DN PREV200100429207
TI The role of MyD88 and TLR4 in the LPS-mimetic activity of Taxol.
AU Byrd-Leifer, Cynthia A.; Block, Ellen F.; Takeda, Kiyoshi; Akira, Shizuo; Ding, Aihao (1)
CS (1) Weill Medical College of Cornell University, 1300 York Avenue, New York, NY, 10021: ahding@med.cornell.edu USA
SO European Journal of Immunology, (August, 2001) Vol. 31, No. 8, pp. 2448-2457. print.
ISSN: 0014-2980.
DT Article
LA English
SL English
AB Taxol can mimic bacterial lipopolysaccharide (LPS) by activating mouse macrophages in a cell cycle-independent, LPS antagonist-inhibitable manner. Macrophages from C3H/HeJ mice, which have a spontaneous mutation in Toll-like receptor 4 (TLR4), are hyporesponsive to both LPS and Taxol, suggesting that LPS and Taxol may share a signaling pathway involving TLR4. To determine whether TLR4 and its interacting adaptor molecule MyD88 are necessary for Taxol's LPS mimetic actions, we examined Taxol responses of primary macrophages from genetically defective mice lacking either TLR4 (C57BL/10ScNCr) or MyD88 (MyD88 knockout). When stimulated with Taxol, macrophages from wild-type mice responded robustly by secreting both TNF and NO, while macrophages from either ***TLR4*** - ***deficient*** C57BL/10ScNCr mice or MyD88 knockout mice produced only minimal amounts of TNF and NO. Taxol-induced NF-kappaB-driven luciferase activity was reduced after transfection of RAW 264.7 macrophages with a dominant negative version of mouse MyD88. Taxol-induced microtubule-associated protein kinase (MAPK) activation and NF-kappaB nuclear translocation were absent from TLR4-null macrophages, but were preserved in MyD88 knockout macrophages with a slight delay in kinetics. Neither Taxol-induced NF-kappaB activation, nor IkappaB degradation was affected by the presence of phosphatidylinositol 3-kinase inhibitors. These results suggest that Taxol and LPS not only share a TLR4/MyD88-dependent pathway in generating inflammatory mediators, but also share a TLR4-dependent/MyD88-independent pathway leading to activation of MAPK and NF-kappaB.

L5 ANSWER 26 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:3353 BIOSIS
DN PREV200200003353
TI Regulation of LPS-mediated CNS gene expression in ***TLR4*** - ***deficient*** C3H/HeJ mice.
AU Chakravarty, S. (1); Herkenham, M. (1)
CS (1) Section on Functional Neuroanatomy, NIMH, Bethesda, MD USA
SO Society for Neuroscience Abstracts, (2001) Vol. 27, No. 2, pp. 2239. print.
Meeting Info.: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295.
DT Conference
LA English
AB Lipopolysaccharide (LPS) derived from gram-negative bacteria mediates its potent inflammatory effect through the activation of toll-like receptor-4 (TLR4) expressed predominantly on macrophages and monocytes. C3H/HeJ mice lack TLR4 and are hyporesponsive to the cellular and behavioral effects of LPS. We used mutant C3H/HeJ and wild type C3H/HeN mice to compare inflammatory and neural responses to LPS at a cellular level in vivo. This approach allowed us to delineate the key pathways that couple the initial cellular recognition of LPS to systemic consequences primarily in the CNS. Mice were challenged with LPS (1 mg/kg i.p.) and killed at 0.5, 2, or 6 h. Serum cytokine fluxes were monitored by ELISA, and pro-inflammatory or neural activation markers in the brain were assayed with in situ hybridization and immunohistochemistry. TLR4 mutants did not upregulate serum TNF-alpha levels in response to LPS but induced IL-1beta to levels similar to wild type. Though the HeJ mice lacked any symptoms of sickness behavior, they had a significant but transient upregulation of transcripts for the pro-inflammatory markers IL-1beta, IkappaBalpha and CD14 in circumventricular organs and meninges. In contrast, mRNA induction of COX-2 and neuronal c-fos were almost totally abrogated in these animals. We therefore demonstrate persistence of components of LPS signaling in TLR4 mutant mice that allows transcription of a subset of pro-inflammatory genes, but fails to support the potent systemic response to LPS. Our results suggest an essential role of TLR4 in induction of COX-2 and highlight the significance of prostaglandin synthesis in the initiation of neural effects of LPS.

L5 ANSWER 27 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 18
AN 2002298521 EMBASE
TI TIRAP: An adapter molecule in the Toll signaling pathway.
AU Horng T.; Barton G.M.; Medzhitov R.
CS R. Medzhitov, Howard Hughes Medical Institute, Section of Immunobiology,

Yale University School of Medicine, New Haven, CT 06520, United States. ruslan@yale.edu
SO Nature Immunology, (2001) 2/9 (835-841).
Refs: 19
ISSN: 1529-2908 CODEN: NIAMCZ
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB Mammalian Toll-like receptors (TLRs) recognize conserved products of microbial metabolism and activate NF-.kappa.B and other signaling pathways through the adapter protein MyD88. Although some cellular responses are completely abolished in MyD88- ***deficient*** mice, ***TLR4*** , but not TLR9, can activate NF-.kappa.B and mitogen-activated protein kinases and induce dendritic cell maturation in the absence of MyD88. These differences suggest that another adapter must exist that can mediate MyD88-independent signaling in response to TLR4 ligation. We have identified and characterized a Toll-interleukin I receptor (TIR) domain-containing adapter protein (TIRAP) and have shown that it controls activation of MyD88-independent signaling pathways downstream of TLR4. We have also shown that the double-stranded RNA-binding protein kinase PKR is a component of both the TIRAP- and MyD88-dependent signaling pathways.

L5 ANSWER 28 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002298519 EMBASE
TI TIRAP: How toll receptors fraternize.
AU Henneke P.; Golenbock D.T.
CS D.T. Golenbock, Department of Medicine, Division of Infectious Diseases, Univ. Massachusetts Medical School, Worcester, MA 01655, United States. douglas.golenbock@umassmed.edu
SO Nature Immunology, (2001) 2/9 (828-830).
Refs: 15
ISSN: 1529-2908 CODEN: NIAMCZ
CY United States
DT Journal; Article
FS 022 Human Genetics
029 Clinical Biochemistry
LA English
SL English
AB Although some cellular responses induced by TLRs are abolished in MyD88-***deficient*** mice, ***TLR4*** , unlike TLR9, can still induce activation of NF-.kappa.B and MAPKs. The discovery of a cytoplasmic adapter protein for TLR4, called TIRAP, helps explain this phenomenon.

L5 ANSWER 29 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:273442 BIOSIS
DN PREV200100273442
TI Roles of toll-like receptor agonists in macrophage responses to M. tuberculosis.
AU Fenton, Matthew J. (1); Means, Terry K. (1); Jones, Bryan W. (1); Vogel, Stefanie N.
CS (1) Boston University School of Medicine, 80 East Concord St., Boston, MA, 02118-2394 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A650. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB We previously showed that viable M. tuberculosis (Mtb) bacilli contain distinct ligands that activate cells via the mammalian Toll-like receptors TLR2 and TLR4. We now show that over-expression of dominant-negative TLR2 and TLR4 mutant proteins in macrophages could partially block Mtb-induced NF-kappaB activation, and together, could block virtually all Mtb-induced NF-kappaB. The importance of TLR4 in host responses was demonstrated by the finding that ***TLR4*** - ***deficient*** C3H/HeJ mice were more susceptible to lethal mycobacterial infection compared with normal C3H/OuJ mice. We also observed that the lipid A-like antagonist E5531 specifically inhibited TLR4-dependent Mtb-induced cellular responses. E5531 could substantially block LPS- and Mtb-induced TNF-alpha production in both RAW264.7 murine macrophages and primary human alveolar macrophages (AMO).
In contrast, E5531 did not inhibit Mtb-induced nitric oxide (NO) production in RAW264.7 cells and AMO. We also found that E5531 was capable of inhibiting Mtb-induced macrophage apoptosis in AMO. This effect was secondary to the inhibition of TNF-alpha production by E5531. Using primary peritoneal macrophages from TLR2- and ***TLR4*** - ***deficient*** animals, we found that Mtb-induced NO production was comparable to that generated by normal control cells. This suggests that TLR2 and TLR4 agonists are not responsible for Mtb-induced NO production by macrophages. Lastly, we demonstrated that a dominant-negative MyD88 mutant could block Mtb-induced activation of the TNF-alpha promoter, but not the iNOS promoter, in murine macrophages. Because MyD88 mediates downstream signaling initiated by all known TLR proteins, our data suggest that Mtb-induced TNF-alpha production is at least partially dependent on TLR4 signaling, whereas Mtb-induced NO production is TLR-independent.

L5 ANSWER 30 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:520582 BIOSIS
DN PREV200200520582
TI The role of Toll-like receptor 2 and 4 for the induction of cytokines by Candida albicans.
AU Netea, M. G. (1); Van der Meer, J. W. M. (1); Kullberg, B. (1)
CS (1) University Medical Center, Nijmegen Netherlands
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 370. print.
Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, Illinois, USA September 22-25, 2001
DT Conference
LA English
AB Background: Disseminated candidiasis represents an increased cause of morbidity and mortality, especially in the immunocompromised hosts. Recent studies have suggested that the Toll-like receptors (TLRs), and especially TLR2 and TLR4, represent the main class of pattern-recognition receptors involved in sensing the presence of invading microorganisms. The aim of the present study was to investigate the role of TLR2 and TLR4 for the stimulation of the proinflammatory and antiinflammatory cytokines by Candida albicans. Methods: When freshly isolated peripheral blood mononuclear cells (PBMC) were stimulated in vitro for 24h with heat-killed C. albicans (107 colony forming units/ml), significant amounts of the proinflammatory cytokines tumor necrosis factor-alpha (TNF) and interleukin-1beta (IL-1) and of the antiinflammatory cytokine IL-10 were produced, as measured by specific RIA or ELISA. Results: Incubation of PBMC with either anti-TLR4 or anti-CD14 blocking antibodies did not influence the production of cytokines induced by C. albicans (p>0.05). Likewise, induction of TNF and IL-1 by C. albicans was similar in ***TLR4*** - ***deficient*** C3H/HeJ mice and control C3H/HeN mice (0.49+-0.11 vs 0.43+-0.14 ng/ml and 0.38+-0.12 vs. 0.40+-0.09, p>0.05, respectively). However, incubation of PBMC with an anti-TLR2 blocking antibody significantly inhibited the production of TNF (2.57+-0.89 vs. 5.23+-1.32 ng/ml, p<0.05), IL-1 (0.86+-0.36 vs. 3.13+-1.17, p<0.05), and IL-10 (26+-10 vs. 71+-10 pg/ml, p<0.05). Conclusions: Induction of pro- and antiinflammatory cytokines by C. albicans involves stimuli mediated by TLR2, but not TLR4 and CD14. These data indicate that the TLR2 pathway is essential for signalling transduction by C. albicans.

L5 ANSWER 31 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2001:885063 CAPLUS
DN 136:367949
TI Identification of Toll-like receptor 4 (Tlr4) as the sole conduit for LPS signal transduction: Genetic and evolutionary studies
AU Beutler, Bruce; Du, Xin; Poltorak, Alexander
CS Department of Immunology, The Scripps Research Institute, La Jolla, CA, 92037, USA
SO Journal of Endotoxin Research (2001), 7(4), 277-280
CODEN: JENREB; ISSN: 0968-0519
PB Maney Publishing
DT Journal; General Review
LA English
AB A review discussing the identification of toll-like receptor 4 as a result of positional cloning work involving the C3H/HeJ and C57BL/10ScCr mouse strains. Each of these strains is known to be profoundly resistant to LPS. Tlr4 is the sole gene in the Lps crit. region and a point mutation modifies the Tlr4 cytoplasmic domain in C3H/HeJ mice. A ***deletion*** removes the entire ***Tlr4*** coding region in C57BL/10ScCr mice. The significant role of Tlr4 in LPS signaling is confirmed by the anal. of mice with a ***Tlr4*** ***knockout*** mutation. Topics discussed include the other mols. that are proposed as LPS signal transducers; the implication of the identity of the LPS transducer in innate immunity in general; and the nature of genetic variation at Tlr4.
RE.CNT 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 32 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
19
AN 2001:337308 BIOSIS
DN PREV200100337308
TI Toll-like receptor 4 is involved in the mechanism of early alcohol-induced liver injury in mice.
AU Uesugi, Takehiko (1); Froh, Matthias; Arteel, Gavin E.; Bradford, Blair U.; Thurman, Ronald G.
CS (1) Department of Pharmacology, Laboratory of Hepatobiology and Toxicology, University of North Carolina at Chapel Hill, Mary Ellen Jones Building, Chapel Hill, NC, 27599-7365: uesugi@med.unc.edu USA
SO Hepatology, (July, 2001) Vol. 34, No. 1, pp. 101-108. print.
ISSN: 0270-9139.
DT Article
LA English
SL English
AB Chronic alcohol administration increases gut-derived endotoxin in the portal blood, which activates Kupffer cells and causes liver injury. Mice (C3H/HeJ) with mutations in toll-like receptor 4 (TLR4) are hyporesponsive to endotoxin. To test the hypothesis that TLR4 is involved in early alcohol-induced liver injury, the long-term intragastric ethanol feeding protocol developed by Tsukamoto and French for rats was adapted to mice. Animals with nonfunctional TLR4 and wild-type mice (C3H/HeOuJ) were

compared. Two-month-old female mice were fed a high-fat liquid diet with either ethanol or isocaloric maltose-dextrin as control continuously for 4 weeks. There was no difference in mean urine alcohol concentrations between the groups. Dietary alcohol significantly increased liver-to-body weight ratios and serum alanine transaminase (ALT) levels in wild-type mice (109+-18 U/L) over high-fat controls (40+-3 U/L), effects that were blunted significantly in mice with a mutation of TLR4 (55+-9 U/L). While no significant pathologic changes were observed in high-fat controls, dietary ethanol caused steatosis, mild inflammation, and focal necrosis in wild-type animals (pathology score=5.2+-1.2). These pathologic changes were significantly lower in ***TLR4*** - ***deficient*** mice fed ethanol (score=2.0+-1.3). Endotoxin levels in the portal vein were increased significantly after 4 weeks in both groups fed ethanol. Moreover, ethanol increased tumor necrosis factor alpha (TNF-alpha) mRNA expression in wild-type, but not in ***TLR4*** - ***deficient*** , mice. These data are consistent with the hypothesis that Kupffer cell activation by endotoxin via TLR4 is involved in early alcohol-induced liver injury.

L5 ANSWER 33 OF 50 CAPLUS COPYRIGHT 2003 ACS
AN 2000:900804 CAPLUS
DN 134:52290
TI TLR4 variants associated with endotoxin hyporesponsiveness in humans and its therapeutic uses
IN Lorenz, Eva; Schwartz, David A.; Schutte, Brian C.
PA University of Iowa Research Foundation, USA
SO PCT Int. Appl., 97 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 2

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000077204	A1	20001221	WO 2000-US15723	20000608
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2002173001	A1	20021121	US 2001-10066	20011207
PRAI US 1999-329515	A2	19990610		
WO 2000-US15723	A1	20000608		

AB The invention provides variants of human gene TLR4 (encoding the toll-like receptor-4) which affect responsiveness to inhaled lipopolysaccharide (LPS). The studies show that common, co-segregating missense mutations (Asp299Gly and Thr399Ile) affecting the extracellular domain of the TLR4 receptor are assocd. with a blunted response to inhaled LPS in humans. Genetic evidence are provided to demonstrate common mutations in TLR4 are assocd. with differences in LPS responsiveness in humans, and gene-sequence changes can alter the ability of the host to respond to environmental stress. The invention provides methods to identify polymorphisms at the human TLR4 locus, as well as methods to identify individuals at risk of indications that increase their morbidity and mortality.
RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L5 ANSWER 34 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
20
AN 2002:440045 BIOSIS
DN PREV200200440045
TI Maturation of human dendritic cells by cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guerin: Involvement of Toll-like receptors.
AU Tsuji, Shoutaro; Matsumoto, Misako; Takeuchi, Osamu; Akira, Shizuo; Azuma, Ichiro; Hayashi, Akira; Toyoshima, Kumao; Seya, Tsukasa (1)
CS (1) Department of Immunology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Higashinari-ku, Osaka, 537: tseya@mail.mc.pref.osaka.jp Japan
SO Infection and Immunity, (December, 2000) Vol. 68, No. 12, pp. 6883-6890. print.
ISSN: 0019-9567.
DT Article
LA English
AB The constituents of mycobacteria are an effective immune adjuvant, as observed with complete Freund's adjuvant. In this study, we demonstrated that the cell wall skeleton of Mycobacterium bovis bacillus Calmette-Guerin (BCG-CWS), a purified noninfectious material consisting of peptidoglycan, arabinogalactan, and mycolic acids, induces maturation of human dendritic cells (DC). Surface expression of CD40, CD80, CD83, and CD86 was increased by BCG-CWS on human immature DC, and the effect was similar to those of interleukin-1beta (IL-1beta), tumor necrosis factor alpha (TNF-alpha), heat-killed BCG, and viable BCG. BCG-CWS induced the secretion of TNF-alpha, IL-6, and IL-12 p40. CD83 expression was increased by a soluble factor secreted from BCG-CWS-treated DC and was completely inhibited by monoclonal antibodies against TNF-alpha. BCG-CWS-treated DC stimulated extensive allogeneic mixed lymphocyte reactions. The level of TNF-alpha secreted through BCG-CWS was partially suppressed in murine macrophages with no Toll-like receptor 2 (TLR 2) or TLR4 and was completely lost in TLR2 and ***TLR4*** double- ***deficient*** macrophages. These results suggest that the BCG-CWS induces TNF-alpha secretion from DC via TLR2 and TLR4 and that the secreted TNF-alpha induces the maturation of DC per se.

L5 ANSWER 35 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 21
AN 2000404596 EMBASE
TI Cutting edge: TLR2-deficient and MyD88-deficient mice are highly susceptible to Staphylococcus aureus infection.
AU Takeuchi O.; Hoshino K.; Akira S.
CS Dr. S. Akira, Department of Host Defense, Res. Inst. for Microbial Diseases, Osaka University, 3-I Yamada-oka, Osaka 565-0871, Japan. sakira@biken.osaka-u.ac.jp
SO Journal of Immunology, (15 Nov 2000) 165/10 (5392-5396). Refs: 24
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Toll-like receptor (TLR) family acts as pattern recognition receptors for pathogen-specific molecular patterns. We previously showed that TLR2 recognizes Gram-positive bacterial components whereas TLR4 recognizes LPS, a component of Gram-negative bacteria. MyD88 is shown to be an adaptor molecule essential for TLR family signaling. To investigate the role of TLR family in host defense against Gram-positive bacteria, we infected TLR2- and MyD88-deficient mice with Staphylococcus aureus. Both TLR2- and MyD88-deficient mice were highly susceptible to S. aureus infection, with more enhanced susceptibility in MyD88-deficient mice. Peritoneal macrophages from MyD88-deficient mice did not produce any detectable levels of cytokines in response to S. aureus. In contrast, TLR2-deficient macrophages produced reduced, but significant, levels of the cytokines, and ***TLR4*** - ***deficient*** macrophages produced the same amounts as wild-type cells, indicating that S. aureus is recognized not only by TLR2, but also by other TLR family members except for TLR4.

L5 ANSWER 36 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
22
AN 2000:400605 BIOSIS
DN PREV200000400605
TI Toll-like receptor 4-deficient mice have reduced bone destruction following mixed anaerobic infection.
AU Hou, Linda; Sasaki, Hajime; Stashenko, Philip (1)
CS (1) Department of Cytokine Biology, Forsyth Institute, 140 The Fenway, Boston, MA, 02115 USA
SO Infection and Immunity, (August, 2000) Vol. 68, No. 8, pp. 4681-4687. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB C3H/HeJ mice have an impaired ability to respond to lipopolysaccharide (LPS) due to a mutation in the gene that encodes Toll-like receptor 4 (TLR4). The effect of ***TLR4*** ***deficiency*** on host responses to endodontic infections is unknown. In the present study, we compared periapical bone destruction, sepsis, and inflammatory cytokine production in LPS-hyporesponsive C3H/HeJ and wild-type control C3H/HeOuJ mice. The mandibular first molars of both strains were subjected to pulpal exposure and infection with a mixture of four anaerobic pathogens, Prevotella intermedia, Fusobacterium nucleatum, Streptococcus intermedius, and Peptostreptococcus micros. At sacrifice on day 21, ***TLR4*** - ***deficient*** C3H/HeJ mice had significantly reduced periapical bone destruction compared to wild-type C3H/HeOuJ mice ($P < 0.001$). The decreased bone destruction in C3H/HeJ correlated with reduced expression of the bone resorptive cytokines interleukin 1alpha (IL-alpha) ($P < 0.01$) and IL-1beta ($P < 0.05$) as well as the proinflammatory cytokine IL-12 ($P < 0.05$). No significant differences were seen in the levels of gamma interferon, tumor necrosis factor alpha (TNF-alpha), or IL-10 between the two strains. The expression of IL-1alpha, IL-1beta, TNF-alpha, IL-10, and IL-12 were all significantly reduced in vitro in macrophages from both ***TLR4*** - ***deficient*** C3H/HeJ and C57BL/10ScNCr strains, compared to wild-type controls. Notably, the responses of ***TLR4*** - ***deficient*** macrophages to both gram-positive and gram-negative bacteria were similarly reduced. Neither C3H/HeJ nor C3H/HeOuJ mice exhibited orofacial abscess development or infection dissemination as determined by splenomegaly or cachexia. We conclude that intact TLR function mediates increased proinflammatory responses and bone destruction in response to mixed anaerobic infections.

L5 ANSWER 37 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
23
AN 2000:533299 BIOSIS
DN PREV200000533299
TI Recognition of CpG DNA is mediated by signaling pathways dependent on the adaptor protein MyD88.
AU Schnare, Markus; Holt, Agnieszka Czopik; Takeda, Kiyoshi; Akira, Shizuo; Medzhitov, Ruslan (1)

CS (1) Section of Immunobiology, Yale University School of Medicine, New Haven, CT, 06520 USA
SO Current Biology, (21 September, 2000) Vol. 10, No. 18, pp. 1139-1142. print.
ISSN: 0960-9822.
DT Article
LA English
SL English
AB The innate immune system evolved to recognize conserved microbial products, termed pathogen-associated molecular patterns (PAMPs), which are invariant among diverse groups of microorganisms. PAMPs are recognized by a set of germ-line encoded pattern recognition receptors (PRRs). Among the best characterized PAMPs are bacterial lipopolysaccharide (LPS), peptidoglycan (PGN), mannans, and other constituents of bacterial and fungal cell walls, as well as bacterial DNA. Recognition of bacterial DNA is the most enigmatic of these, as it depends on a particular sequence motif, called the CpG motif, in which an unmethylated CpG present in a particular sequence context accounts for a potent immunostimulatory activity of CpG DNA. Receptor(s) of the innate immune system that mediate recognition of CpG DNA are currently unknown. Here, we report that recognition of CpG DNA requires MyD88, an adaptor protein involved in signal transduction by the Toll-like receptors (TLRs), essential components of innate immune recognition in both Drosophila and mammals. Signaling induced by CpG DNA was found to be unaffected in cells ***deficient*** in TLR2 or ***TLR4*** , suggesting that some other member of the Toll family mediates recognition of bacterial DNA.

L5 ANSWER 38 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:315015 BIOSIS
DN PREV200100315015
TI LPS and TNF-alpha induced host dendritic cell maturation are not required in vivo for GVHD induction.
AU Schwarz, D. (1); Emerson, S.; Shlomchik, M. J. (1); Shlomchik, W. D. (1)
CS (1) Yale University School of Medicine, New Haven, CT USA
SO Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 768a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000 American Society of Hematology
. ISSN: 0006-4971.
DT Conference
LA English
SL English
AB Lipopolysaccharide (LPS), TNF-alpha, and IL-1 have been implicated in GVHD
pathogenesis, but which precise cellular events mediate these effects is unknown. We have established a murine GVHD model in which 1) radiation resistant recipient APCs are absolutely required; and 2) recipient dendritic cells (DC) are sufficient to induce GVHD (Science, vol. 285, p. 412-415, and ASH Abstract, submitted, 2000). Since LPS, TNF-a and IL-1 each have been shown to induce DC maturation in vitro and DC migration from tissues to lymphoid organs in vivo, we sought to define the contribution of these molecules to DC function in our GVHD model. In these studies T cell depleted C3H.SW (H-2b) bone marrow (T-BM) +/- purified C3H.SW CD8 cells was used to reconstitute irradiated normal B6, B10 or mutant strains deficient in their response to LPS, TNF-alpha or IL-1. B10.ScNCR mice, which harbor a naturally occurring ***deletion*** of ***TLR4*** , and whose susceptibility to endotoxin, and LPS induced DC maturation and B cell activation is greatly reduced actually developed more severe GVHD than TLR4+/+ B10/J mice (15 mice per group), and equivalent GVHD to B10.ScNCR X B10/J F1 mice (15 mice/group). Consistent with these in vivo results, in vitro BM derived DC maturation of F1 DCs was reduced as compared to wild type controls at low concentrations of LPS. To evaluate the role of TNF-alpha induced DC maturation, we used B6 TNFR1-/- fwdarwwt B6(Ly5.1) BM chimeras as transplant recipients to avoid potential effects of GVHD target tissues lacking TNFR1 receptors. DC replacement in these chimeras was greater than 97% as assessed by flow cytometry using the allelic difference at Ly5 to distinguish donor from host. When these chimeras underwent a second GVHD inducing transplant they suffered GVHD similar to that seen in B6fwdarwB6 (Ly5.1) recipients. These data argue against a major role for endotoxin induced maturation of host DCs in GVHD pathogenesis, and instead supports the hypothesis that LPS effects in GVHD are on donor cells (Cooke et al, 1998, JCI, 102; 1882-91). The increased GVHD seen in B 10.ScNCR further suggests that accelerated DC maturation and death may actually limit the efficiency of T cell priming and intensity of GVHD. These results also indicate that TNF-alpha induced DC maturation is not required. In this model, DC maturation either occurs via other yet to be defined mechanisms or immature DCs have sufficient T cell stimulatory activity to initiate GVHD, or both. The role of IL-1 type I receptors in host DC function in GVHD induction is currently under investigation and available new data will be presented at the meeting.

L5 ANSWER 39 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
24
AN 2000:419912 BIOSIS
DN PREV200000419912
TI Immune cell activation by bacterial CpG-DNA through myeloid differentiation marker 88 and tumor necrosis factor receptor-associated factor (TRAF)6.
AU Haecker, Hans (1); Vabulas, Ramunas M.; Takeuchi, Osamu; Hoshino, Katsuaki; Akira, Shizuo; Wagner, Hermann
CS (1) Institute of Medical Microbiology, Immunology and Hygiene, Technische Universitaet Muenchen, Trogerstr. 9, D-81675, Munich Germany
SO Journal of Experimental Medicine, (August 21, 2000) Vol. 192, No. 4, pp. 595-600. print.
ISSN: 0022-1007.
DT Article
LA English
SL English
AB Transition of immature antigen presenting cells (APCs) to the state of professional APCs is essential for initiation of cell-mediated immune responses to pathogens. Signal transduction via molecules of the Toll-like receptor (TLR)/interleukin 1 receptor (IL-1R) pathway is critical for activation of APCs either by pathogen-derived pattern ligands like lipopolysaccharides (LPS) or by CD40 ligation through T helper cells. The capacity of bacterial DNA (CpG-DNA) to induce APCs to differentiate into professional APCs represents an interesting discovery. However, the signaling pathways involved are poorly understood. Here we show that CpG-DNA activates the TLR/IL-1R signaling pathway via the molecules myeloid differentiation marker 88 (MyD88) and tumor necrosis factor receptor-associated factor 6 (TRAF6), leading to activation of kinase of the IkappaB kinase complex and the c-jun NH2-terminal kinases. Moreover, cells of TLR2- and ***TLR4*** - ***deficient*** mice are activated by CpG-DNA, whereas cells of MyD88-deficient mice do not respond. The data suggest that CpG-DNA initiates signaling via the TLR/IL-1R pathway in APCs in a manner similar to LPS and to T helper cell-mediated CD40 ligation. Activation of the TLR/IL-1R signaling pathway by foreign bacterial DNA may be one way to initiate innate defense mechanisms against infectious pathogens in vivo.

L5 ANSWER 40 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 25
AN 2000030179 EMBASE
TI Cutting edge: Preferentially the R-stereoisomer of the mycoplasmal lipopeptide macrophage-activating lipopeptide-2 activates immune cells through a toll-like receptor 2- and MyD88-dependent signaling pathway.
AU Takeuchi O.; Kaufmann A.; Grote K.; Kawai T.; Hoshino K.; Morr M.; Muhlradt P.F.; Akira S.
CS Dr. S. Akira, Department of Host Defense, Res. Inst. for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan. sakira@biken.osaka-u.ac.jp
SO Journal of Immunology, (15 Jan 2000) 164/2 (554-557).
Refs: 29
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Mycoplasmas and their membranes are potent activators of macrophages, the active principle being lipoproteins and lipopeptides. Two stereoisomers of the mycoplasmal lipopeptide macrophage-activating lipopeptide-2 (MALP-2) differing in the configuration of the lipid moiety were synthesized and compared in their macrophage-activating potential, the R-MALP being >100 times more active than the S-MALP in stimulating the release of cytokines, chemokines, and NO. To assess the role of the Toll-like receptor (TLR) family in mycoplasmal lipopeptide signaling, the MALP-2-mediated responses were analyzed using macrophages from wild-type, TLR2-, ***TLR4*** -, and MyD88- ***deficient*** mice. TLR2- and MyD88-deficient cells showed severely impaired cytokine productions in response to R- and S-MALP. The MALP-induced activation of intracellular signaling molecules was fully dependent on both TLR2 and MyD88. There was a strong preference for the R-MALP in the recognition by its functional receptor, TLR2.

L5 ANSWER 41 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
26
AN 2000:315990 BIOSIS
DN PREV200000315990
TI Toll-like receptor 4 imparts ligand-specific recognition of bacterial lipopolysaccharide.
AU Lien, Egil; Means, Terry K.; Heine, Holger; Yoshimura, Atsutoshi; Kusumoto, Shoichi; Fukase, Koichi; Fenton, Matthew J.; Oikawa, Masato; Qureshi, Nilofer; Monks, Brian; Finberg, Robert W.; Ingalls, Robin R.; Golenbock, Douglas T. (1)
CS (1) Maxwell Finland Laboratory for Infectious Diseases, 774 Albany Street, Boston, MA, 02118 USA
SO Journal of Clinical Investigation, (February, 2000) Vol. 105, No. 4, pp. 497-504. print.
ISSN: 0021-9738.
DT Article
LA English
SL English
AB Lipopolysaccharide (LPS) is the main inducer of shock and death in Gram-negative sepsis. Recent evidence suggests that LPS-induced signal transduction begins with CD14-mediated activation of 1 or more Toll-like receptors (TLRs). The lipid A analogues lipid IVa and Rhodobacter sphaeroides lipid A (RSLA) exhibit an uncommon species-specific pharmacology. Both compounds inhibit the effects of LPS in human cells but display LPS-mimetic activity in hamster cells. We transfected human TLR4 or human TLR2 into hamster fibroblasts to determine if either of these LPS signal transducers is responsible for the species-specific pharmacology. RSLA and lipid IVa strongly induced NF-kappaB activity and IL-6 release in Chinese hamster ovary fibroblasts expressing CD14(CHO/CD14), but these

compounds antagonized LPS antagonists in CHO/CD 14 fibroblasts that overexpressed human TLR4. No such antagonism occurred in cells overexpressing human TLR2. We cloned TLR4 from hamster macrophages and found that human THP-1 cells expressing the hamster TLR4 responded to lipid IVa as an LPS mimetic, as if they were hamster in origin. Hence, cells heterologously overexpressing TLR4 from different species acquired a pharmacological phenotype with respect to recognition of lipid A substructures that corresponded to the species from which the ***TLR4*** ***transgene*** originated. These data suggest that TLR4 is the central lipid A-recognition protein in the LPS receptor complex.

L5 ANSWER 42 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
27
AN 2001:128408 BIOSIS
DN PREV200100128408
TI Pattern recognition receptors TLR4 and CD14 mediate response to respiratory syncytial virus.
AU Kurt-Jones, Evelyn A. (1); Popova, Lana; Kwinn, Laura; Haynes, Lia M.; Jones, Les P.; Tripp, Ralph A.; Walsh, Edward E.; Freeman, Mason W.; Golenbock, Douglas T.; Anderson, Larry J.; Finberg, Robert W.
CS (1) Department of Medicine, University of Massachusetts Medical School, Worcester, MA, 01605: evelyn.kurt-jones@umassmed.edu USA
SO Nature Immunology, (November, 2000) Vol. 1, No. 5, pp. 398-401. print. ISSN: 1529-2908.
DT Article
LA English
SL English
AB The innate immune system contributes to the earliest phase of the host defense against foreign organisms and has both soluble and cellular pattern recognition receptors for microbial products. Two important members of this receptor group, CD14 and the Toll-like receptor (TLR) pattern recognition receptors, are essential for the innate immune response to components of Gram-negative and Gram-positive bacteria, mycobacteria, spirochetes and yeast. We now find that these receptors function in an antiviral response as well. The innate immune response to the fusion protein of an important respiratory pathogen of humans, respiratory syncytial virus (RSV), was mediated by TLR4 and CD14. RSV persisted longer in the lungs of infected ***TLR4*** - ***deficient*** mice compared to normal mice. Thus, a common receptor activation pathway can initiate innate immune responses to both bacterial and viral pathogens.

L5 ANSWER 43 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
28
AN 2000:114435 BIOSIS
DN PREV200000114435
TI Cellular responses to bacterial cell wall components are mediated through MyD88-dependent signaling cascades.
AU Takeuchi, Osamu; Takeda, Kiyoshi; Hoshino, Katsuaki; Adachi, Osamu; Ogawa, Tomohiko; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871 Japan
SO International Immunology, (Jan., 2000) Vol. 12, No. 1, pp. 113-117. ISSN: 0953-8178.
DT Article
LA English
SL English
AB MyD88 is an adaptor molecule essential for signaling via the Toll-like receptor (TLR)/IL-1 receptor family. TLR4 is a member of the TLR family and a point mutation in the Tlr4 gene causes hyporesponsiveness to lipopolysaccharide (LPS) in C3H/HeJ mice. We have previously shown that both ***TLR4*** - and MyD88- ***deficient*** mice are hyporesponsive to LPS. In this study we examined the responsiveness of these two knockout mice to various bacterial cell wall components. Cells from ***TLR4*** - ***deficient*** mice responded to several kinds of LPS, peptidoglycan and crude cell wall preparation from Gram-positive bacteria and mycobacterial lysates. In contrast, macrophages and splenocytes from MyD88-deficient mice did not respond to any of the bacterial components we tested. These results show that MyD88 is essential for the cellular response to bacterial cell wall components.

L5 ANSWER 44 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2000:534500 BIOSIS
DN PREV200000534500
TI Unresponsiveness of ***TLR4*** - and MyD88- ***deficient*** mice to chemically synthesized bacterial lipid A.
AU Asai, Y. (1); Yamamoto, H. (1); Takeuchi, O.; Akira, S.; Ogawa, T. (1)
CS (1) Department of Oral Microbiology, School of Dentistry, Asahi University, Gifu Japan
SO Journal of Endotoxin Research, (2000) Vol. 6, No. 2, pp. 105. print. Meeting Info.: 6th Conference of the International Endotoxin Society Paris, France August 24-27, 2000 ISSN: 0968-0519.
DT Conference
LA English
SL English

L5 ANSWER 45 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
29
AN 2000:387932 BIOSIS
DN PREV200000387932
TI Limits of ***deletion*** spanning ***Tlr4*** in C57BL/10ScCr mice.
AU Poltorak, Alexander; Smirnova, Irina; Clisch, Renee; Beutler, Bruce (1)
CS (1) University of Texas Southwestern Medical Center and Howard Hughes Medical Institute, 5323 Harry Hines Boulevard, Dallas, TX, 75235-9050 USA
SO Journal of Endotoxin Research, (2000) Vol. 6, No. 1, pp. 51-56. print. ISSN: 0968-0519.
DT Article
LA English
SL English
AB Proceeding from our observation that LPS-unresponsive mice of the strain C57BL/10ScCr mice fail to express the Tlr4 gene (Poltorak A, He X. Smirnova I et al. Defective LPS signaling in C3H/HeJ and C57BL/10ScCr mice: mutations in Tlr4 gene. Science 1998; 282: 2085), we have defined the exact limits of a ***deletion*** encompassing ***Tlr4*** in the C57BL/10ScCr genome. The deletion removes 74723 bp of DNA, with reference to the control strain 129/J (from which the complete sequence of the Tlr4 locus was obtained). There is no inserted element, and no re-arrangement of the chromosome (e.g. inversion or translocation) in the immediate region of ***Tlr4*** ; the ***deletion*** removes only one recognizable gene. Hence, other immunological anomalies that have been identified in C57BL/10ScCr mice (a non-healing phenotype in Leishmania inoculation and failure to produce interferon-gamma in response to numerous microbial infections) must be ascribed to one of two causes. Mutation(s) at other loci may be responsible for these defects. Alternatively, ***Tlr4*** locus ***deletion*** may have phenotypic consequences that exceed the well known blockade of LPS signal transduction.

L5 ANSWER 46 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
30
AN 1999:237255 BIOSIS
DN PREV199900237255
TI Toll-like receptor-4 mediates lipopolysaccharide-induced signal transduction.
AU Chow, Jesse C. (1); Young, Donna W.; Golenbock, Douglas T.; Christ, William J.; Gusovsky, Fabian
CS (1) Eisai Research Institute, 100 Research Dr., Wilmington, MA, 01887 USA
SO Journal of Biological Chemistry, (April 16, 1999) Vol. 274, No. 16, pp. 10689-10692. ISSN: 0021-9258.
DT Article
LA English
SL English
AB TLR4 is a member of the recently identified Toll-like receptor family of proteins and has been putatively identified as Lps, the gene necessary for potent responses to lipopolysaccharide in mammals. In order to determine whether TLR4 is involved in lipopolysaccharide-induced activation of the nuclear factor-kappaB (NF-kappaB) pathway, HEK 293 cells were transiently transfected with human TLR4 cDNA and an NF-kappaB-dependent luciferase reporter plasmid followed by stimulation with lipopolysaccharide/CD14 complexes. The results demonstrate that lipopolysaccharide stimulates NF-kappaB-mediated gene expression in cells transfected with the TLR4 gene in a dose- and time-dependent fashion. Furthermore, E5531, a lipopolysaccharide antagonist, blocked ***TLR4*** -mediated ***transgene*** activation in a dose-dependent manner (IC50 apprx30 nM). These data demonstrate that TLR4 is involved in lipopolysaccharide signaling and serves as a cell-surface co-receptor for CD14, leading to lipopolysaccharide-mediated NF-kappaB activation and subsequent cellular events.

L5 ANSWER 47 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999236037 EMBASE
TI Cutting edge: Functional characterization of the effect of the C3H/HeJ defect in mice that lack an Lps(n) gene: In vivo evidence for a dominant negative mutation.
AU Vogel S.N.; Johnson D.; Perera P.-Y.; Medvedev A.; Lariviere L.; Qureshi S.T.; Malo D.
CS Dr. S.N. Vogel, Dept. of Microbiology and Immunology, Uniformend Svcs. Univ. of Hlth. Sci., 4301 Jones Bridge Road, Bethesda, MD 20814-4799, United States. vogel@bob.usuf2.usuhs.mil
SO Journal of Immunology, (15 May 1999) 162/10 (5666-5670). Refs: 34 ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 022 Human Genetics
026 Immunology, Serology and Transplantation
LA English
SL English
AB A point mutation in the Tlr4 gene, which encodes Toll-like receptor 4, has recently been proposed to underlie LPS hyporesponsiveness in C3H/HeJ mice (Lps(d)). The data presented herein demonstrate that F1 progeny from crosses between mice that carry a .apprx.9-cM deletion of chromosome 4 (including ***deletion*** of Lps(***Tlr4***)) and C3H/HeJ mice (i.e., Lps0 x Lps(d) F1 mice) exhibit a pattern of LPS sensitivity, measured by TNF activity, that is indistinguishable from that exhibited bY Lps(n) x Lps(d) F1 progeny and whose average response is 'intermediate' to parental responses. Thus, these data provide clear functional support for the hypothesis that the C3H/HeJ defect exerts a dominant negative effect

on LPS sensitivity; however, expression of a normal Toll-like receptor 4 molecule is apparently not required.

L5 ANSWER 48 OF 50 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 31
AN 1999235870 EMBASE
TI Cutting edge: Toll-like receptor 4 (***TLR4***)- ***deficient*** mice are hyporesponsive to lipopolysaccharide evidence for TLR4 as the Lps gene product.
AU Hoshino K.; Takeuchi O.; Kawai T.; Sanjo H.; Ogawa T.; Takeda Y.; Takeda K.; Akira S.
CS Dr. S. Akira, Department of Biochemistry, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, Hyogo 663-8501, Japan. akira@hyo-med.ac.jp
SO Journal of Immunology, (1 Apr 1999) 162/7 (3749-3752).
Refs: 16
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB The human homologue of Drosophila Toll (hToll), also called Toll-like receptor 4 (TLR4), is a recently cloned receptor of the IL-1/Toll receptor family. Interestingly, the TLR4 gene has been localized to the same region to which the Lps locus (endotoxin unresponsive gene locus) is mapped. To examine the role of TLR4 in LPS unresponsiveness, we have generated mice lacking TLR4. Macrophages and B cells from ***TLR4*** - ***deficient*** mice did not respond to LPS. All these manifestations were quite similar to those of LPS- hyporesponsive C3H/HeJ mice. Furthermore, C3H/HeJ mice have, in the cytoplasmic portion of TLR4, a single point mutation of the amino acid that is highly conserved among the IL-1/Toll receptor family. Over-expression of wild-type TLR but not the mutant TLR4 from C3H/HeJ mice activated NF-.kappa.B. Taken together, the present study demonstrates that TLR4 is the gene product that regulates LPS response.

L5 ANSWER 49 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
32
AN 1999:187689 BIOSIS
DN PREV199900187689
TI Endotoxin-tolerant mice have mutations in Toll-like receptor 4 (Tlr4.
AU Qureshi, Salman T.; Lariviere, Line; Leveque, Gary (1); Clermont, Sophie; Moore, Karen J.; Gros, Philippe; Malo, Danielle (1)
CS (1) Centre for the Study of Host Resistance, Montreal General Hospital, 1650 Cedar Avenue, Rm. L11-144, Montreal, Quebec, H3G 1A4 Canada
SO Journal of Experimental Medicine, (Feb. 15, 1999) Vol. 189, No. 4, pp. 615-625.
ISSN: 0022-1007.
DT Article
LA English
AB Bacterial lipopolysaccharide (LPS) provokes a vigorous, generalized proinflammatory state in the infected host. Genetic regulation of this response has been localized to the Lps locus on mouse chromosome 4, through study of the C3H/HeJ and C57BL/10ScCr inbred strains. Both C3H/HeJ and C57BL/10ScCr mice are homozygous for a mutant Lps allele (Lpsd/d) that confers hyporesponsiveness to LPS challenge, and therefore exhibit natural tolerance to its lethal effects. Genetic and physical mapping of 1,345 backcross progeny segregating this mutant phenotype confined Lps to a 0.9-cM interval spanning 1.7 Mb. Three transcription units were identified within the candidate interval, including Toll-like receptor 4 (Tlr4), part of a protein family with members that have been implicated in LPS-induced cell signaling. C3H/HeJ mice have a point mutation within the coding region of the Tlr4 gene, resulting in a nonconservative substitution of a highly conserved proline by histidine at codon 712, whereas C57BL/10ScCr mice exhibit a ***deletion*** of ***Tlr4*** . Identification of distinct mutations involving the same gene at the Lps locus in two different hyporesponsive inbred mouse strains strongly supports the hypothesis that altered Tlr4 function is responsible for endotoxin tolerance.

L5 ANSWER 50 OF 50 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
33
AN 2000:2855 BIOSIS
DN PREV200000002855
TI Differential roles of TLR2 and TLR4 in recognition of gram-negative and gram-positive bacterial cell wall components.
AU Takeuchi, Osamu; Hoshino, Katsuaki; Kawai, Taro; Sanjo, Hideki; Takada, Haruhiko; Ogawa, Tomohiko; Takeda, Kiyoshi; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Suita Japan
SO Immunity, (Oct., 1999) Vol. 11, No. 4, pp. 443-451.
ISSN: 1074-7613.
DT Article
LA English
SL English
AB Toll-like receptor (TLR) 2 and TLR4 are implicated in the recognition of various bacterial cell wall components, such as lipopolysaccharide (LPS). To investigate in vivo roles of TLR2, we generated TLR2-deficient mice. In contrast to LPS unresponsiveness in ***TLR4*** - ***deficient*** mice, TLR2- ***deficient*** mice responded to LPS to the same extent as wild-type mice. TLR2-deficient macrophages were hyporesponsive to several Gram-positive bacterial cell walls as well as Staphylococcus aureus peptidoglycan. ***TLR4*** - ***deficient*** macrophages lacked the response to Gram-positive lipoteichoic acids. These results demonstrate that TLR2 and TLR4 recognize different bacterial cell wall components in vivo and TLR2 plays a major role in Gram-positive bacterial recognition.

=> d his

(FILE 'HOME' ENTERED AT 15:06:21 ON 06 JAN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:06:35 ON 06 JAN 2003
L1 1254 S TLR4
L2 772 S TLR2
L3 539 S MYD88
L4 105 S L1 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR D
L5 50 DUP REM L4 (55 DUPLICATES REMOVED)

=> s l2 (3a) (knockout or knock out or deficien? or transgen? or delet?)
L6 87 L2 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR
DELET?)

=> dup rem l6
PROCESSING COMPLETED FOR L6
L7 39 DUP REM L6 (48 DUPLICATES REMOVED)

=> s l7 not l5
L8 28 L7 NOT L5

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 28 ANSWERS - CONTINUE? Y/(N):y

L8 ANSWER 1 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:22734 BIOSIS
DN PREV200300022734
TI Toll-like receptor 2 is required for innate, but not acquired, host defense to Borrelia burgdorferi.
AU Wooten, R. Mark; Ma, Ying; Yoder, R. Alyson; Brown, Jeanette P.; Weis, John H.; Zachary, James F.; Kirschning, Carsten J.; Weis, Janis J. (1)
CS (1) Department of Pathology, University of Utah School of Medicine, 50 North Medical Drive, Salt Lake City, UT, 84132, USA: janis.weis@path.utah.edu USA
SO Journal of Immunology, (January 1 2002) Vol. 168, No. 1, pp. 348-355. print.
ISSN: 0022-1767.
DT Article
LA English
AB Borrelia burgdorferi lipoproteins activate inflammatory cells through Toll-like receptor 2 (TLR2), suggesting that TLR2 could play a pivotal role in the host response to B. burgdorferi. TLR2 does play a critical role in host defense, as infected TLR2-/- mice harbored up to 100-fold more spirochetes in tissues than did TLR2+/+ littermates. Spirochetes persisted at extremely elevated levels in ***TLR2*** - ***deficient*** mice for at least 8 wk following infection. Infected TLR2-/- mice developed normal Borrelia-specific Ab responses, as measured by quantity of Borrelia-specific Ig isotypes, the kinetics of class switching to IgG, and the complexity of the Ags recognized. These findings indicate that the failure to control spirochete levels in tissues is not due to an impaired acquired immune response. While macrophages from TLR2-/- mice were not responsive to lipoproteins, they did respond to nonlipoprotein components of sonicated spirochetes. These TLR2-independent responses could play a role during the inflammatory response to B. burgdorferi, as infected TLR2-/- mice developed greater ankle swelling than wild-type littermates. Thus, while TLR2-dependent signaling pathways play a major role in the innate host defense to B. burgdorferi, both inflammatory responses and the development of the acquired humoral response can occur in the absence of TLR2.

L8 ANSWER 2 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:7418 BIOSIS
DN PREV200300007418
TI Cutting edge: Immune stimulation by neisserial porins is toll-like receptor 2 and MyD88 dependent.
AU Massari, Paola; Henneke, Philipp; Ho, Yu; Latz, Eicke; Golenbock, Douglas T.; Wetzler, Lee M. (1)
CS (1) Department of Medicine, Division of Infectious Diseases, Boston University School of Medicine, 650 Albany Street, Boston, MA, 02118, USA: lwetzler@bu.edu USA
SO Journal of Immunology, (February 15 2002) Vol. 168, No. 4, pp. 1533-1537. print.
ISSN: 0022-1767.
DT Article
LA English
AB The immunopotentiating activity of neisserial porins, the major outer membrane protein of the pathogenic Neisseria, is mediated by its ability to stimulate B cells and up-regulate the surface expression of B7-2. This ability is dependent on MyD88 and Toll-like receptor (TLR)2 expression, as demonstrated by a lack of a response by B cells from MyD88 or ***TLR2*** ***knockout*** mice to the porins. Using previously described

TLR2-dependent reporter constructs, these results were confirmed and were shown to be due to induction of NF-kappaB nuclear translocation. This is the first demonstration of known vaccine adjuvant to stimulate immune cells via TLR2.

L8 ANSWER 3 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:597148 BIOSIS
DN PREV200200597148
TI Toll-like receptor (TLR) signaling in response to Aspergillus fumigatus.
AU Mambula, S. S. (1); Sau, K. (1); Henneke, P.; Golenbock, D. T.; Levitz, S. M. (1)
CS (1) Boston University School of Medicine, Boston, MA USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 217-218. http://www.asmusa.org/mtgsrc/generalmeeting.htm. print.
Meeting Info.: 102nd General Meeting of the American Society for Microbiology Salt Lake City, UT, USA May 19-23, 2002 American Society for Microbiology
. ISSN: 1060-2011.
DT Conference
LA English
AB Aspergillus fumigatus causes life-threatening infections in patients with qualitative and quantitative defects in phagocytic function. Here, we examined the contribution of Toll-like receptor (TLR)-2, TLR4 and CD14 to signaling in response to the three forms of A. fumigatus encountered during human disease: resting conidia (RC), swollen conidia (SC) and hyphae (H). The human monocytic cell line, THP-1, stably transfected with CD14 (THP1-CD14) and control cells stably transfected with the empty vector (THP1-RSV) were transiently transfected with a plasmid containing a nuclear factor kappa B (NFkappa B) -dependent luciferase reporter gene. Upon stimulation with RC, SC, and H, there was a significantly higher luciferase response of the THP1-CD14 cells to all three growth phases when compared to the THP1-RSV cells. Similarly, RC, SC and H stimulated greater release of tumor necrosis factor-alpha (TNF-alpha) from THP1-CD14 cells compared with THP1-RSV cells. Compared to elicited peritoneal macrophages obtained from wild type C57Bl/6 mice, macrophages from ***TLR2*** ***knock*** ***out*** mice produced significantly less TNF-alpha following stimulation with RC and H, but similar amounts following stimulation with SC. In contrast, compared with macrophages from congenic C3H/OuJ mice, macrophages from TLR4 mutant C3H/HeJ mice secreted significantly less TNF-alpha following stimulation with SC but similar amounts in response to RC and H. The adapter protein, MyD88, links TLR to the intracellular signaling cascade. Stimulation of macrophages from MyD88 knockout mice with RC, SC and H resulted in levels of TNF-alpha that were less than 10% of the levels seen following stimulation of macrophages obtained from wild type, C57BL/6 mice. These data, taken together, suggest that optimal macrophage signaling in response to A. fumigatus is contingent upon the cell surface receptors CD14, TLR2, and TLR4, acting via the adapter protein MyD88. Moreover, the TLR utilized by the macrophage varies depending upon the specific growth phase of the fungus.

L8 ANSWER 4 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:596994 BIOSIS
DN PREV200200596994
TI Immune stimulation by neisserial porins is TLR2 and MyD88 dependent.
AU Wetzler, L. M. (1); Henneke, P.; Ho, Y. (1); Latz, E.; Golenbock, D.; Massari, P. (1)
CS (1) Boston University School of Medicine, Boston, MA USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 189. http://www.asmusa.org/mtgsrc/generalmeeting.htm. print.
Meeting Info.: 102nd General Meeting of the American Society for Microbiology Salt Lake City, UT, USA May 19-23, 2002 American Society for Microbiology
. ISSN: 1060-2011.
DT Conference
LA English
AB Neisserial porins are the major protein components of the neisserial outer membranes. They have been shown to act as immune adjuvants and to potentiate the immune response against certain antigens and to elicit a T cell dependent immune response to T cell independent antigens. Their effect is mediated by the up-regulation of the co-stimulatory molecule B7-2 (CD86) on the surface of B cells and dendritic cells. TLRs have been associated with the innate immune response to microbial structures such as LPS, lipoproteins, CpG DNA, etc. Once TLRs are engaged by such microbial products, the dimerization and recruitment of the adaptor molecule MyD88 is induced, which leads to NF-6B nuclear translocation. The involvement of Toll-like receptor 2 (TLR2), which has an extraordinarily broad repertoire of ligands, in the effect of neisserial porin PorB on the immune system was investigated. Two TLR2 negative, NF-6B-dependent, reporter cell lines were used in this study. When TLR2 expression was restored, the cells responded to stimulation by PorB. B cells from ***TLR2*** ***knockout*** mice failed to increase surface expression of B7-2 and class II MHC upon treatment with PorB, as opposed to B cells from wild type mice. This demonstrates that up-regulation by PorB of B7-2 and class II MHC surface expression is TLR2 dependent. We then investigated the involvement of MyD88 in the response to neisserial porins, and found that B cells from MyD88 knockout mice also failed to be stimulated by neisserial porins. In conclusion, our results suggest a central role for TLR2 in porin recognition, supporting the hypothesis that the effect of neisserial porins on the immune system requires the presence of TLR2 and MyD88.

L8 ANSWER 5 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:584966 BIOSIS
DN PREV200200584966
TI Amphotericin B stimulates proinflammatory cytokine production via Toll-like receptors and CD14-dependent signal transduction pathways.
AU Sau, K. (1); Mambula, S. (1); Henneke, P.; Golenbock, D. T.; Levitz, S. M. (1)
CS (1) Boston University School of Medicine, Boston, MA USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (2002) Vol. 102, pp. 83-84. http://www.asmusa.org/mtgsrc/generalmeeting.htm. print.
Meeting Info.: 102nd General Meeting of the American Society for Microbiology Salt Lake City, UT, USA May 19-23, 2002 American Society for Microbiology
. ISSN: 1060-2011.
DT Conference
LA English
AB The antifungal drug Amphotericin B (AmB) is the gold standard for the treatment of life-threatening fungal infections. Despite the excellent efficacy of AmB against many fungal pathogens, the drug often is not well tolerated due to a plethora of side effects. Many of the side effects of AmB, including fever and chills, suggest AmB stimulates a proinflammatory response from innate immune cells. Because AmB is a product of the Gram positive bacterium Streptomyces nodosus, we hypothesized that innate immune cells interact with AmB via Toll-like receptors (TLRs), innate immune pattern recognition receptors used by cells to recognize microbial products. TLR signaling results in the activation of NF-kB and MAP kinases via an adapter protein, MyD88, to induce the production of the inflammatory mediator, TNF-a. In this study TLR and/or CD14 (a GPI-anchored receptor often associated with TLR4 and TLR2 complexes) stably-transfected cells lines were assayed for NF-kB-driven reporter activity following AmB stimulation. Peritoneal macrophages from TLR-mutated or -deficient mice were also assayed for cytokine production (by ELISA) following AmB stimulation in vitro. AmB stimulated NF-kB-driven reporter activity from CHO cells stably transfected with CD14 and TLR2 as well as CD14 and TLR4. CD14- or empty vector-transfected CHO cells did not produce significant reporter activity in response to AmB stimulation. Elicited peritoneal macrophages (PMf) of C57BL/6 MyD88 knockout mice and C57BL/6 ***TLR2*** ***knockout*** mice did not produce TNF-a in response to AmB stimulation whereas PMf from C57BL/6 WT and C3H/HeOuJ (TLR4 WT) mice produced increased levels of TNF-a in response to AmB stimulation. PMf from C3H/HeJ (TLR4-mutated) mice produced reduced levels of TNF-a in response to AmB slimulation. Taken together, these findings indicate a role for TLR2 and CD14 and, possibly TLR4 in the response of innate immune cells to AmB. AmB stimulation of TLRs in complex with CD14 results in the production of a pro-inflammatory mediator that may explain, in part, the molecular basis for the proinflammatory response induced in patients following AmB administration.

L8 ANSWER 6 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:577151 BIOSIS
DN PREV200200577151
TI Yersinia V-antigen exploits toll-like receptor 2 and CD14 for interleukin 10-mediated immunosuppression.
AU Sing, Andreas; Rost, Dagmar; Tvardovskaia, Natalia; Roggenkamp, Andreas; Wiedemann, Agnes; Kirschning, Carsten J.; Aepfelbacher, Martin; Heesemann, Juergen (1)
CS (1) Max von Pettenkofer-Institut fuer Hygiene und Medizinische Mikrobiologie, Pettenkoferstrasse 9a, 80336, Muenchen: heesemann@m3401.mpk.med.uni-muenchen.de Germany
SO Journal of Experimental Medicine, (October 21, 2002) Vol. 196, No. 8, pp. 1017-1024. http://www.jem.org. print.
ISSN: 0022-1007.
DT Article
LA English
AB A characteristic of the three human-pathogenic Yersinia spp. (the plague agent Yersinia pestis and the enteropathogenic Yersinia pseudotuberculosis and Yersinia enterocolitica) is the expression of the virulence (V)-antigen (LcrV). LcrV is a released protein which is involved in contact-induced secretion of yersinia antihost proteins and in evasion of the host's innate immune response. Here we report that recombinant LcrV signals in a CD14- and toll-like receptor 2 (TLR2)-dependent fashion leading to immunosuppression by interleukin 10 induction. The impact of this immunosuppressive effect for yersinia pathogenesis is underlined by the observation that ***TLR2*** - ***deficient*** mice are less susceptible to oral Y. enterocolitica infection than isogenic wild-type animals. In summary, these data demonstrate a new ligand specificity of TLR-2, as LcrV is the first known secreted and nonlipidated virulence-associated protein of a Gram-negative bacterium using TLR2 for cell activation. We conclude that yersiniae might exploit host innate pattern recognition molecules and defense mechanisms to evade the host immune response.

L8 ANSWER 7 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:561043 BIOSIS
DN PREV200200561043
TI MyD88-dependent but Toll-like receptor 2-independent innate immunity to Listeria: No role for either in macrophage listericidal activity.

AU Edelson, Brian T.; Unanue, Emil R. (1)
CS (1) Department of Pathology and Immunology, Washington University School of Medicine, 660 South Euclid Avenue, Box 8118, Saint Louis, MO, 63110: unanue@pathbox.wustl.edu USA
SO Journal of Immunology, (October 1, 2002) Vol. 169, No. 7, pp. 3869-3875. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB We have assessed the requirements for Toll-like receptor (TLR) signaling in vivo during early infection with Listeria monocytogenes. Mice ***deficient*** for ***TLR2*** , a receptor required for the recognition of Gram-positive peptidoglycan, showed equivalent Listeria resistance to wild-type mice. However, mice deficient for MyD88, an adaptor molecule used by all TLRs, showed profound susceptibility with 3-4 logs greater Listeria burden and severe spleen and liver pathology at day 3 postinfection. Listeria-infected MyD88-deficient mice also showed markedly diminished IFN-gamma, TNF-alpha, and NO responses, despite evidence of macrophage activation and up-regulation of MHC class II molecules. We demonstrate that although minor MyD88-independent responses to live Listeria do occur, these are insufficient for normal host defense. Lastly, we performed experiments in vitro in which macrophages ***deficient*** in ***TLR2*** or MyD88 were directly infected with Listeria. Although TLR signaling was required for macrophage NO and cytokine production in response to Listeria, handling and direct killing of Listeria by activated macrophages occurred by TLR2- and MyD88-independent mechanisms.

L8 ANSWER 8 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:555118 BIOSIS
DN PREV200200555118
TI ***TLR2*** ***deficient*** mice are highly susceptible to Streptococcus pneumoniae meningitis.
AU Echchannaoui, H. (1); Rajacic, Z. (1); Ferracin, F. (1); Landmann, R. (1)
CS (1) Div. of Infectious Diseases, Dept. Research, Univ. Hosp., Basel Switzerland
SO Abstracts of the Interscience Conference on Antimicrobial Agents and Chemotherapy, (2001) Vol. 41, pp. 71. print.
Meeting Info.: 41st Annual Meeting of the Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago, Illinois, USA September 22-25, 2001
DT Conference
LA English
AB Toll-like receptors (TLR) are involved in the recognition of the bacterial cell surface and thus, play a key role in antibacterial host defense. Recently, TLR2 has been shown to recognize cell wall components of Gram-positive bacteria in vitro. In order to elucidate the in vivo role of TLR2 against live Gram-positive bacteria, wild-type (wt) and ***TLR2*** - ***deficient*** (-/-) mice were injected intracerebrally with 3000 colony forming units (cfu) of Streptococcus (S.) pneumoniae serotype 3. Clinical and inflammatory parameters were investigated between 6h and 5 days after infection. TLR2-/- mice showed higher severity scores than wt mice 3 days after S. pneumoniae infection. They also showed a lower survival rate (0% vs. 60% after 5 days) despite the fact that both wt and TLR2-/- mice had the same number of leukocytes (1.105 leukocytes/mul CSF) and bacteria (5.104 cfu/mul CSF) in cerebrospinal fluid (CSF) after 24h. Moreover blood cfu were not significantly different in wt and TLR2-/- mice. These observations were confirmed by the fact that antibiotic treatment with ceftriaxone starting 18h after S. pneumoniae infection rescued all wt mice whereas only 60% of TLR2-/- survived after treatment. Interestingly, TLR2-/- mice presented higher TNFa levels (7500 vs 1000 pg/ml) in the CSF after 24h. Therefore the in vitro response towards live S. pneumoniae was compared in peritoneal macrophages obtained from wt and TLR2-/- mice. In TLR2-/- cells, the expected hyporesponsiveness to Gram-positive bacterial cell walls contrasted with an increased TNFa (1200 vs 100 pg/ml) and nitric oxide (12 vs 4muM) response upon stimulation with live S. pneumoniae. Our results indicate that the lack of TLR2 is associated with a more pronounced inflammatory response during S. pneumoniae infection. This inflammation could be at the origin of the reduced survival in the TLR2-/- mice.

L8 ANSWER 9 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:541973 BIOSIS
DN PREV200200541973
TI Toll-like receptor 2 contributes to liver injury by Salmonella infection through Fas ligand expression on NKT cells in mice.
AU Shimizu, Hideyuki; Matsuguchi, Tetsuya (1); Fukuda, Yoshihide; Nakano, Isao; Hayakawa, Tetsuo; Takeuchi, Osamu; Akira, Shizuo; Umemura, Masayuki; Suda, Takashi; Yoshikai, Yasunobu
CS (1) Laboratory of Host Defense and Germfree Life, Research Institute for Disease Mechanism and Control, Nagoya University School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya, 466-8550: tmatsugu@med.nagoya-u.ac.jp Japan
SO Gastroenterology, (October, 2002) Vol. 123, No. 4, pp. 1265-1277. http://www.gastrojournal.org/. print.
ISSN: 0016-5085.
DT Article
LA English
AB Background and Aims: Toll-like receptors (TLRs) for bacterial constitutes are expressed not only by phagocytes but also by some subsets of T cells. We previously reported that natural killer T cells (NKT cells) play an important role in liver injury induced by Salmonella infection. In the present study, we investigated whether TLRs on NKT cells are involved in Salmonella-induced liver injury. Methods: Gene expression of TLR2 was examined in sorted natural killer, NKT, and T cells from livers of naive mice by the reverse-transcription polymerase chain reaction method. Serum alanine aminotransferase level and FasL expression on liver lymphocytes were examined in ***TLR2*** - ***deficient*** (***TLR2*** -/-) and FasL- ***deficient*** gld/gld mice before and after intraperitoneal inoculation of Salmonella choleraesuis 31N-1 using an enzyme-linked immunosorbent assay and flow cytometry. Results: TLR2 gene was abundantly expressed by NKT cells freshly isolated from naive mice. FasL expression on liver NKT cells increased in TLR2+/- mice but not in TLR2-/- mice after Salmonella infection. Serum alanine aminotransferase level was significantly lower in the TLR2-/- and gld/gld mice than in the control mice after infection. Conclusions: TLR2 may contribute to liver injury induced by Salmonella infection via FasL induction on liver NKT cells.

L8 ANSWER 10 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:538080 BIOSIS
DN PREV200200538080
TI Toll-like receptor 2-deficient mice are highly susceptible to Streptococcus pneumoniae meningitis because of reduced bacterial clearing and enhanced inflammation.
AU Echchannaoui, Hakim; Frei, Karl; Schnell, Christian; Leib, Stephen L.; Zimmerli, Werner; Landmann, Regine (1)
CS (1) Div. of Infectious Diseases, Dept. of Research, University Hospital, Hebelstr. 20, CH-4031, Basel: regine.landmann@unibas.ch Switzerland
SO Journal of Infectious Diseases, (15 September, 2002) Vol. 186, No. 6, pp. 798-806. http://www.journals.uchicago.edu/JID/home.html. print.
ISSN: 0022-1899.
DT Article
LA English
AB Toll-like receptor-2 (TLR2) mediates host responses to gram-positive bacterial wall components. TLR2 function was investigated in a murine Streptococcus pneumoniae meningitis model in wild-type (wt) and ***TLR2*** - ***deficient*** (***TLR2*** -/-) mice. ***TLR2*** -/- mice showed earlier time of death than wt mice (P<.02). Plasma interleukin-6 levels and bacterial numbers in blood and peripheral organs were similar for both strains. With ceftriaxone therapy, none of the wt but 27% of the TLR2-/- mice died (P<.04). Beyond 3 hours after infection, TLR2-/- mice had higher bacterial loads in brain than did wt mice, as assessed with luciferase-tagged S. pneumoniae by means of a Xenogen-CCD (charge-coupled device) camera. After 24 h, tumor necrosis factor activity was higher in cerebrospinal fluid of TLR2-/- than wt mice (P<.05) and was related to increased blood-brain barrier permeability (Evans blue staining, P<.02). In conclusion, the lack of TLR2 was associated with earlier death from meningitis, which was not due to sepsis but to reduced brain bacterial clearing, followed by increased intrathecal inflammation.

L8 ANSWER 11 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:529207 BIOSIS
DN PREV200200529207
TI Role of chlamydial heat shock protein 60 in the stimulation of innate immune cells by Chlamydia pneumoniae.
AU da Costa, Clarissa Prazeres; Kirschning, Carsten J.; Busch, Dirk; Duerr, Susanne; Jennen, Luise; Heinzmann, Ulrich; Prebeck, Sigrid; Wagner, Hermann; Miethke, Thomas (1)
CS (1) Institute of Medical Microbiology, Immunology and Hygiene Technical University of Munich, Trogerstr. 9, D-81675, Munich: Thomas.Miethke@lrz.tu-muenchen.de Germany
SO European Journal of Immunology, (September, 2002) Vol. 32, No. 9, pp. 2460-2470. http://www.wiley-vch.de/publish/en/journals/alphabeticIndex/2040/?sID=87ce709e9d93384f19ebcbf2d13f6116. print.
ISSN: 0014-2980.
DT Article
LA English
AB Chlamydia pneumoniae stimulates potently maturation of and cytokine secretion by bone marrow-derived dendritic cells (BMDDC). BMDDC responses depend mainly on Toll-like receptor (TLR) 2 and to a minor extent on TLR4. We demonstrate here using C. pneumoniae in an infectious model with the replication-permissive epithelial cell line HEp2 that HSP60 is produced in substantial amounts in chlamydial inclusions during infection. Electron microscopy of chlamydial inclusions revealed that HSP60 was mainly associated with reticulate bodies, but was also located in between the different chlamydial developmental forms. Supernatants of permissive HEp2 cells infected with C. pneumoniae contained soluble chlamydial HSP60 as demonstrated by Western blotting and were able to stimulate BMDDC of wild-type mice. The stimulatory capacity of culture supernatants correlated with the presence of chlamydial HSP60. In contrast, BMDDC from TLR4-mutant mice crossed to ***TLR2*** - ***deficient*** mice were not stimulated by the culture supernatant, indicating that chlamydial HSP60 but not cytokines, possibly secreted by infected HEp2 cells, are responsible for the observed stimulation of BMDDC. Purified recombinant HSP60 from C. pneumoniae stimulated BMDDC in a TLR2- and TLR4-dependent
fashion similar to the whole microorganism. In summary, these data suggest chlamydial HSP60 as an important mediator of inflammatory responses during infection with C. pneumoniae.

L8 ANSWER 12 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

AN 2002:452705 BIOSIS
DN PREV200200452705
TI Activation of Toll-like receptor 2 in acne triggers inflammatory cytokine responses.
AU Kim, Jenny; Ochoa, Maria-Teresa; Krutzik, Stephan R.; Takeuchi, Osamu; Uematsu, Satoshi; Legaspi, Annaliza J.; Brightbill, Hans D.; Holland, Diana; Cunliffe, William J.; Akira, Shizuo; Sieling, Peter A.; Godowski, Paul J.; Modlin, Robert L. (1)
CS (1) Division of Dermatology, School of Medicine, University of California, Los Angeles, 10833 Le Conte Avenue, 52-121 Center for Health Sciences, Los Angeles, CA, 90095: rmodlin@mednet.ucla.edu USA
SO Journal of Immunology, (August 1, 2002) Vol. 169, No. 3, pp. 1535-1541. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB One of the factors that contributes to the pathogenesis of acne is Propionibacterium acnes; yet, the molecular mechanism by which P. acnes induces inflammation is not known. Recent studies have demonstrated that microbial agents trigger cytokine responses via Toll-like receptors (TLRs). We investigated whether TLR2 mediates P. acnes-induced cytokine production in acne. Transfection of TLR2 into a nonresponsive cell line was sufficient for NF-kB activation in response to P. acnes. In addition, peritoneal macrophages from wild-type, TLR6 knockout, and TLR1 ***knockout*** mice, but not ***TLR2*** ***knockout*** mice, produced IL-6 in response to P. acnes. P. acnes also induced activation of IL-12 p40 promoter activity via TLR2. Furthermore, P. acnes induced IL-12 and IL-8 protein production by primary human monocytes and this cytokine production was inhibited by anti-TLR2 blocking Ab. Finally, in acne lesions, TLR2 was expressed on the cell surface of macrophages surrounding pilosebaceous follicles. These data suggest that P. acnes triggers inflammatory cytokine responses in acne by activation of TLR2. As such, TLR2 may provide a novel target for treatment of this common skin disease.

L8 ANSWER 13 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:442102 BIOSIS
DN PREV200200442102
TI Hyporesponsiveness to vaccination with Borrelia burgdorferi OspA in humans and in TLR1- and ***TLR2*** - ***deficient*** mice.
AU Alexopoulou, Lena; Thomas, Venetta; Schnare, Markus; Lobet, Yves; Anguita, Juan; Schoen, Robert T.; Medzhitov, Ruslan; Fikrig, Erol; Flavell, Richard A. (1)
CS (1) Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT: erol.fikrig@yale.edu, richard.flavell@yale.edu USA
SO Nature Medicine, (August, 2002) Vol. 8, No. 8, pp. 878-884. http://www.nature.com/nm/. print.
ISSN: 1078-8956.
DT Article
LA English
AB The Lyme disease vaccine is based on the outer-surface lipoprotein (OspA) of the pathogen Borrelia burgdorferi, and 95% of vaccine recipients develop substantial titers of antibodies against OspA. Here, we identified seven individuals with very low antibody titers after vaccination (low responders). The macrophages of low responders produced less tumor necrosis factor-alpha and interleukin-6 after OspA stimulation and had lower cell-surface expression of Toll-like receptor (TLR) 1 as compared to normal cells, but normal expression of TLR2. TLRs activate innate responses to pathogens, and TLR2 recognizes lipoproteins and peptidoglycan (PGN). After OspA immunization, mice genetically ***deficient*** in either ***TLR2*** (***TLR2*** -/-) or TLR1 (TLR1-/-) produced low titers of antibodies against OspA. Notably, macrophages from TLR2-/- mice were unresponsive to OspA and PGN, whereas those from TLR1-/- mice responded normally to PGN but not to OspA. These data indicate that TLR1 and TLR2 are required for lipoprotein recognition and that defects in the TLR1/2 signaling pathway may account for human hyporesponsiveness to OspA vaccination.

L8 ANSWER 14 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:413018 BIOSIS
DN PREV200200413018
TI Cutting Edge: Role of toll-like receptor 1 in mediating immune response to microbial lipoproteins.
AU Takeuchi, Osamu; Sato, Shintaro; Horiuchi, Takao; Hoshino, Katsuaki; Takeda, Kiyoshi; Dong, Zhongyun; Modlin, Robert L.; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO Journal of Immunology, (July 1, 2002) Vol. 169, No. 1, pp. 10-14. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB The Toll-like receptor (TLR) family acts as pattern recognition receptors for pathogen-specific molecular patterns (PAMPs). TLR2 is essential for the signaling of a variety of PAMPs, including bacterial lipoprotein/lipopeptides, peptidoglycan, and GPI anchors. TLR6 associates with TLR2 and recognizes diacylated mycoplasmal lipopeptide along with TLR2. We report here that TLR1 associates with TLR2 and recognizes the native mycobacterial 19-kDa lipoprotein along with ***TLR2*** . Macrophages from TLR1- ***deficient*** (TLR1-/-) mice showed impaired proinflammatory cytokine production in response to the 19-kDa lipoprotein and a synthetic triacylated lipopeptide. In contrast, TLR1-/- cells responded normally to diacylated lipopeptide. TLR1 interacts with TLR2 and coexpression of TLR1 and TLR2 enhanced the NF-kappaB activation in response to a synthetic lipopeptide. Furthermore, lipoprotein analogs whose acylation was modified were preferentially recognized by TLR1. Taken together, TLR1 interacts with TLR2 to recognize the lipid configuration of the native mycobacterial lipoprotein as well as several triacylated lipopeptides.

L8 ANSWER 15 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:336973 BIOSIS
DN PREV200200336973
TI Glycosylphosphatidylinositol-anchored mucin-like glycoproteins isolated from Trypanosoma cruzi trypomastigotes induce in vivo leukocyte recruitment dependent on MCP-1 production by IFN-gamma-primed-macrophages.
AU Coelho, Patricia S.; Klein, Andre; Talvani, Andre; Coutinho, Sibele F.; Takeuchi, Osamu; Akira, Shizuo; Silva, Joao S.; Canizzaro, Helia; Gazzinelli, Ricardo T.; Teixeira, Mauro M. (1)
CS (1) Departamento de Bioquimica e Imunologia, Instituto de Ciencias Biologicas, Universidade Federal de Minas Gerais, Av. Antonio Carlos, 6627-Pampulha, 31270-901, Belo Horizonte, MG: mmtex@icb.ufmg.br Brazil
SO Journal of Leukocyte Biology, (May, 2002) Vol. 71, No. 5, pp. 837-844. http://www.jleukbio.org. print.
ISSN: 0741-5400.
DT Article
LA English
AB Glycosylphosphatidylinositol-anchored mucin-like glycoproteins from Trypanosoma cruzi trypomastigotes (tGPI-mucins) activate macrophages in vitro to produce proinflammatory cytokines, chemokines, and nitric oxide. These effects of tGPI-mucins may be important in the ensuing immune response to T. cruzi. Here, we have sought evidence for a role of tGPI-mucins in mediating leukocyte recruitment in vivo. tGPI-mucins are highly effective in promoting cell recruitment in the pleural cavity of mice primed with IFN-gamma-inducing agents but not in naive mice. Maximal recruitment was observed at a dose between 250 and 1250 ng tGPI-mucins. There was a significant elevation in the levels of MCP-1 in the pleural cavity of primed animals injected with tGPI-mucins, and in vivo neutralization of MCP-1 abolished leukocyte recruitment. Pretreatment with anti-MIP-1alpha or anti-RANTES had no effect on the recruitment induced by tGPI-mucins. MCP-1 immunoreactivity was detected in pleural macrophages, and macrophages produced MCP-1 in vitro, especially after priming with IFN-gamma. Finally, tGPI-mucins induced significant leukocyte recruitment in primed C3H/HeJ but not in ***TLR2*** - ***deficient*** mice. Together, our results suggest that T. cruzi-derived GPI-mucins in conjunction with IFN-gamma may drive tissue chemokine production and inflammation and bear a significant role in the pathogenesis of Chagas disease.

L8 ANSWER 16 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:271620 BIOSIS
DN PREV200200271620
TI Toll-like receptor 2 is at least partly involved in the antitumor activity of glycoprotein from Chlorella vulgaris.
AU Hasegawa, Takashi (1); Matsuguchi, Tetsuya; Noda, Kiyoshi; Tanaka, Kuniaki; Kumamoto, Shoichiro; Shoyama, Yukihiro; Yoshikai, Yasunobu
CS (1) Research Laboratories, Chlorella Industry Co., Ltd., 1343 Hisatomi, Chikugo City, Fukuoka, 833-0056: hasegawa@chlorella.co.jp Japan
SO International Immunopharmacology, (March, 2002) Vol. 2, No. 4, pp. 579-589. http://www.elsevier.com/locate/intimp. print.
ISSN: 1567-5769.
DT Article
LA English
AB Toll-like receptors (TLR) are involved in innate immunity by recognizing various bacterial components. We have previously reported that an active substance of ARS-2 purified from the culture medium of Chlorella vulgaris was a glycoprotein with a molecular weight of 63,100 amu and that this glycoprotein expressed antitumor activity, with the protein moiety in ARS-2 being necessary for this antitumor activity. Here, we show that ARS-2 stimulated spleen-adherent cells from C3H/HeJ lacking functional TLR4 to produce interleukin-12 (IL-12) p40, whereas such cytokine production was significantly impaired in ARS-2-stimulated spleen-adherent cells from ***TLR2*** ***knockout*** mice. The overexpression of mouse TLR2 (mTLR2) and mouse CD14 (mCD14) conferred the ARS-2 inducibility of nuclear factor-kappaB activation to human HEK 293 cells. These results suggest that TLR2 signaling is at least partly involved in the antitumor activity of the water-soluble antitumor glycoprotein from C. vulgaris.

L8 ANSWER 17 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:169378 BIOSIS
DN PREV200200169378
TI Extracellular toll-like receptor 2 region containing Ser40-Ile64 but not Cys30-Ser39 is critical for the recognition of Staphylococcus aureus peptidoglycan.
AU Mitsuzawa, Hiroaki; Wada, Ikuo; Sano, Hitomi; Iwaki, Daisuke; Murakami, Seiji; Himi, Tetsuo; Matsushima, Norio; Kuroki, Yoshio (1)
CS (1) Dept. of Biochemistry, Sapporo Medical University School of Medicine, South-1 West-17, Chuo-ku, Sapporo, 060-8556: kurokiy@sapmed.ac.jp Japan

SO Journal of Biological Chemistry, (November 2, 2001) Vol. 276, No. 44, pp. 41350-41356. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Toll-like receptor 2 (TLR2) and CD14 function as pattern recognition receptors for bacterial peptidoglycan (PGN). TLRs and CD14 possess repeats of the leucine-rich motif. To address the role of the extracellular domain of TLR2 in PGN signaling, we constructed CD14/TLR2 chimeras, in which residues 1-356 or 1-323 of CD14 were substituted for the extracellular domain of ***TLR2*** , and five ***deletion*** mutants of ***TLR2*** , in which the progressively longer regions of extracellular ***TLR2*** regions were ***deleted*** . PGN induced NF-kappaB activation in HEK293 cells expressing TLR2 but not in cells expressing CD14/TLR2 chimeras. The cells transfected with a deletion mutant TLR2DELTACys30-Ile64 as well as TLR2DELTACys30-Asp160 and TLR2DELTACys30-Asp305 failed to respond to PGN, indicating the importance of the TLR2 region Cys30-Ile64. Although TLR2DELTACys30-Ser39 conferred cell responsiveness to PGN, the cells expressing TLR2DELTASer40-Ile64 failed to induce NF-kappaB activation. In addition, NF-kappaB activity elicited by PGN was significantly attenuated in the presence of synthetic peptide corresponding to the TLR2 region Ser40-Ile64. From these results, we conclude that; 1) CD14 cannot functionally replace the extracellular domain of TLR2 in PGN signaling; 2) the TLR2 region Cys30-Ser39 is not required for PGN recognition; 3) the TLR2 region containing Ser40-Ile64 is critical for PGN recognition.

L8 ANSWER 18 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:408447 BIOSIS
DN PREV200100408447
TI The role of toll-like receptors (TLRs) in bacteria-induced maturation of murine dendritic cells (DCs): Peptidoglycan and lipoteichoic acid are inducers of DC maturation and require TLR2.
AU Michelsen, Kathrin S.; Aicher, Alexandra; Mohaupt, Mariette; Hartung, Thomas; Dimmeler, Stefanie; Kirschning, Carsten J.; Schumann, Ralf R. (1)
CS (1) Institut fuer Mikrobiologie und Hygiene, Dorotheenstr. 96, 10117, Berlin: ralf.schumann@charite.de Germany
SO Journal of Biological Chemistry, (July 13, 2001) Vol. 276, No. 28, pp. 25680-25686. print.
ISSN: 0021-9258.
DT Article
LA English
SL English
AB Toll-like receptors (TLRs) have been found to be key elements in pathogen recognition by the host immune system. Dendritic cells (DCs) are crucial for both innate immune responses and initiation of acquired immunity. Here we focus on the potential involvement of TLR ligand interaction in DC maturation. ***TLR2*** ***knockout*** mice and mice carrying a TLR4 mutation (C3H/HeJ) were investigated for DC maturation induced by peptidoglycan (PGN), lipopolysaccharide, (LPS), or lipoteichoic acids (LTAs). All stimuli induced maturation of murine bone marrow-derived DCs in control mice. TLR2-/- mice lacked maturation upon stimulation with PGN, as assessed by expression of major histocompatibility complex class II, CD86, cytokine, and chemokine production, fluorescein isothiocyanate-dextran uptake, and mixed lymphocyte reactions, while being completely responsive to LPS. A similar lack of maturation was observed in C3H/HeJ mice upon stimulation with LPS. DC maturation induced by LTAs from two different types of bacteria was severely impaired in TLR2-/-, whereas C3H/HeJ mice responded to LTAs in a manner similar to wild-type mice. We demonstrate that DC maturation is induced by stimuli from Gram-positive microorganisms, such as PGN and LTA, with similar efficiency as by LPS. Finally, we provide evidence that TLR2 and TLR4 interaction with the appropriate ligand is essential for bacteria-induced maturation of DCs.

L8 ANSWER 19 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:397624 BIOSIS
DN PREV200100397624
TI Monocytic cell activation by nonendotoxic glycoprotein from Prevotella intermedia ATCC 25611 its mediated by Toll-like receptor 2.
AU Sugawara, Shunji (1); Yang, Shuhua; Iki, Koichi; Hatakeyama, Junko; Tamai, Riyoko; Takeuchi, Osamu; Akashi, Sachiko; Espevik, Terje; Akira, Shizuo; Takada, Haruhiko
CS (1) Department of Microbiology and Immunology, Tohoku University School of Dentistry, 4-1 Seiryo-machi, Aoba-ku, Sendai, 980-8575: sugawars@mail.cc.tohoku.ac.jp Japan
SO Infection and Immunity, (August, 2001) Vol. 69, No. 8, pp. 4951-4957. print.
ISSN: 0019-9567.
DT Article
LA English
SL English
AB Lipopolysaccharide (LPS) preparations from gram-negative black-pigmented bacteria such as Porphyromonas gingivalis and Prevotella intermedia activate cells from non-LPS-responsive C3H/HeJ mice, but it is still unclear whether this activity is due to the unique structure of LPS or to a minor component(s) responsible for the activity in the preparation. A nonendotoxic glycoprotein with bioactivity against cells from C3H/HeJ mice was purified from a hot phenol-water extract of P. intermedia ATCC 25611 and designated Prevotella glycoprotein (PGP). Treatment of human monocytic THP-1 cells with 22-oxyacalcitriol (OCT) induced maturation and marked expression of CD14 on the cells, but the cells constitutively expressed Toll-like receptor 2 (TLR2) and TLR4 on the cells irrespective of the treatment. PGP induced a high level of interleukin-8 production at doses of 100 ng/ml and higher in OCT-treated THP-1 cells compared with Salmonella LPS, and the production was significantly inhibited by anti-CD14 and anti-TLR2 but not anti-TLR4 antibodies. Consistent with this, ***TLR2*** - ***deficient*** murine macrophages did not respond to PGP. It was also shown that PGP activity on the THP-1 cells was LPS-binding protein dependent and was inhibited by a synthetic lipid A precursor IVA. These results indicate that PGP activates monocytic cells in a CD14- and TLR2-dependent manner.

L8 ANSWER 20 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:299046 BIOSIS
DN PREV200100299046
TI MALP-2, a Mycoplasma lipopeptide with classical endotoxic properties: End of an era of LPS monopoly.
AU Galanos, C. (1); Gumenscheimer, M.; Muehlradt, P. F.; Jirillo, E.; Freudenberg, M. A.
CS (1) Max-Planck-Institut fuer Immunbiologie, Stuebeweg 51, 79108, Freiburg Germany
SO Journal of Endotoxin Research, (2000) Vol. 6, No. 6, pp. 471-476. print.
ISSN: 0968-0519.
DT Article
LA English
SL English
AB Although some activities of LPS are shared by other bacterial components, for half a century LPS has been regarded as unique in displaying many pathophysiological activities. Here we report on a synthetic lipopeptide, MALP-2 from Mycoplasma fermentans, which expresses potent endotoxin-like activity and whose lethal toxicity is comparable to that of LPS. With the exception of the Limulus lysate gelation test, in which MALP-2 was approximately 1000-fold less active than LPS, the synthetic lipopeptide induced all activities tested for, and in most cases to an extent comparable to that of LPS. Unlike LPS, the biological activities of MALP-2 were expressed both in LPS-responder and in LPS-non-responder mice (BALB/c/l, C57BL10/ScCr), indicating that MALP-2 signaling, unlike that of LPS, is not transduced via the Toll-like receptor (Tlr) 4 protein. MALP-2 expressed no toxicity in normal or sensitized ***Tlr2*** ***knockout*** (***Tlr2*** -/-) mice indicating that its toxic activity is induced via Tlr2 signaling. The phenomenology of the lethal shock induced by MALP-2 in normal or sensitized mice, i. e. the kinetics of its development and symptoms of illness exhibited by the treated animals, was very reminiscent of the lethal shock induced by LPS.

L8 ANSWER 21 OF 28 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:269005 BIOSIS
DN PREV200100269005
TI Importance of the amino-terminal region of toll-like receptor 2 extracellular domain in signaling of Staphylococcal peptidoglycan and Streptococcus pneumoniae.
AU Mitsuzawa, Hiroaki (1); Iwaki, Daisuke; Sano, Hitomi (1); Murakami, Seiji (1); Konishi, Masanori (1); Yokota, Shinichi (1); Fujii, Nobuhiro (1); Himi, Tetsuo (1); Kuroki, Yoshio (1)
CS (1) Sapporo Medical University, South-1 West-17, Chuo-ku, Sapporo, 060-8556 Japan
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A648. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Toll-like receptor 2 (TLR2) is a signal transducer for peptidoglycan (PGN) which is the main stimulatory components of Gram positive bacteria. CD14, which does not traverse the plasma membrane, is also known as a pattern recognition receptor for PGN. Extracellular domains of TLRs and CD14 contain repeats of leucine-rich motif. Although CD14 is thought not to directly transmit PGN signaling but to enhance it through TLR2, the precise roles of the extracellular domains of CD14 and TLR2 remain unknown. To address this, we constructed a chimera (CD14/TLR2 chimera) in which the extracellular domain of TLR2 was substituted for that of CD14. In addition, we also constructed five deletion mutants in which the progressively longer regions of extracellular ***TLR2*** domain were ***deleted*** . We then examined the responsiveness to PGN from Staphylococcus aureus and heat-killed Streptococcus pneumoniae by measuring NF-kappaB activity using HEK293 cells transiently transfected with these mutant genes. PGN and heat-killed S. pneumoniae stimulated NF-kappaB reporter activity in wt TLR2- but not CD14/TLR2 chimera-transfected cells. Although the cells transfected with ***deletion*** mutants of ***TLR2*** (DELTA30-64, DELTA30-160, DELTA30-305, DELTA30-449) failed to respond to PGN and S. pneumoniae, those transfected with TLR2DELTA30-39 responded well in a manner dependent upon PGN concentrations. Moreover, neither a single transfection of CD14 nor co-transfection of the ***deletion*** mutants of ***TLR2*** with CD14, conferred the cellular responsiveness on HEK293 cells. From these results, we conclude that; 1) the extracellular domain of CD14 cannot functionally replace that of TLR2 in PGN signaling; 2) an N-terminal of TLR2 region of amino acid residue 40-64 is critical for the recognition of bacterial components.

L8 ANSWER 22 OF 28 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002454449 EMBASE
TI Enhancement of endotoxin activity by muramyldipeptide.
AU Takada H.; Yokoyama S.; Yang S.
CS Dr. H. Takada, Dept. of Microbiology and Immunology, Tohoku Univ. School of Dentistry, 4-1 Seiryo-machi, Aoba-ku, Sendai 980-8575, Japan. dent-ht@mail.cc.tohoku.ac.jp
SO Journal of Endotoxin Research, (2002) 8/5 (337-342).
Refs: 48
ISSN: 0968-0519 CODEN: JENREB
CY United Kingdom
DT Journal; (Short Survey)
FS 004 Microbiology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
052 Toxicology
LA English
SL English
AB Synthetic muramyldipeptide (MDP), the minimum structural moiety of bacterial peptidoglycan for adjuvant and related activities, sensitized mice for two types of lethal shock induced by lipopolysaccharide (LPS): an early anaphylactoid shock and late endotoxin shock. In relation to the late reaction in MDP-primed mice, enhanced production of inflammatory cytokines was induced in response to various bacterial components. MDP showed a priming effect in mice not only when administered parentally but also via the oral route. MDP activated human monocytic THP-1 cells in a CD14-, Toll-like receptor 2 (TLR2)- and TLR4-independent manner to increase expression of MyD88, a common adaptor and signaling molecule for TLRs, and exhibited synergistic cytokine-inducing effects with TLR4 agonists (LPS, synthetic lipid A), TLR2 agonist (synthetic lipopeptide), and TLR9 agonist (bacterial CpG DNA) in THP-1 cells in culture. Consistent with these findings, MDP primed ***TLR2*** ***knockout*** mice as well as wild-type controls, but not TLR4-mutated C3H/HeJ mice, to enhance production of tumor necrosis factor-.alpha. upon stimulation with synthetic lipid A. In contrast to the BCG- and Propionibacterium acnes-priming system, MDP primed mice in an interferon-.gamma.-independent manner. Further studies are required to elucidate the mechanisms of the synthetic and priming activities of MDP for various bacterial components.

L8 ANSWER 23 OF 28 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001438563 EMBASE
TI Novel engagement of CD14 and multiple toll-like receptors by group B streptococci.
AU Henneke P.; Takeuchi O.; Van Strijp J.A.; Guttormsen H.-K.; Smith J.A.; Schromm A.B.; Espevik T.A.; Akira S.; Nizet V.; Kasper D.L.; Golenbock D.T.
CS Dr. D.T. Golenbock, Department of Medicine, Univ. of Massachusetts Med. School, 364 Plantation Street, Worcester, MA 01605, United States. douglas.golenbock@umasssmed.edu
SO Journal of Immunology, (15 Dec 2001) 167/12 (7069-7076).
Refs: 48
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Group B streptococcus (GBS) imposes a major health threat to newborn infants. Little is known about the molecular basis of GBS-induced sepsis. Both heat-inactivated whole GBS bacteria and a heat-labile soluble factor released by GBS during growth (GBS-F) induce nuclear translocation of NF-.kappa.B, the secretion of TNF-.alpha., and the formation of NO in mouse macrophages. Macrophages from mice with a targeted disruption of MyD88 failed to secrete TNF-.alpha. in response to both heat-inactivated whole bacteria and GBS-F, suggesting that Toll-like receptors (TLRs) are involved in different aspects of GBS recognition. Immune cell activation by whole bacteria differed profoundly from that by secreted GBS-F. Whole GBS activated macrophages independently of TLR2 and TLR6, whereas a response to the secreted GBS-F was not observed in macrophages from ***TLR2*** - ***deficient*** animals. In addition to TLR2, TLR6 and CD14 expression were essential for GBS-F responses, whereas TLR1 and TLR4
or MD-2 did not appear to be involved. Heat lability distinguished GBS-F from peptidoglycan and lipoproteins. GBS mutants deficient in capsular polysaccharide or .beta.-hemolysin had GBS-F activity comparable to that of wild-type streptococci. We suggest that CD14 and TLR2 and TLR6 function as coreceptors for secreted microbial products derived from GBS and that cell wall components of GBS are recognized by TLRs distinct from TLR1, 2, 4, or 6.

L8 ANSWER 24 OF 28 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001078894 EMBASE
TI Mycoplasma fermentans lipoprotein M161Ag-induced cell activation is mediated by toll-like receptor 2: Role of N-terminal hydrophobic portion in its multiple functions.
AU Nishiguchi M.; Matsumoto M.; Takao T.; Hoshino M.; Shimonishi Y.; Tsuji S.; Begum N.A.; Takeuchi O.; Akira S.; Toyoshima K.; Seya T.
CS Dr. T. Seya, Department of Immunology, Osaka Medical Center, Cancer and Cardiovascular Diseases, Higashinari-ku, Osaka 537-8511, Japan. tseya@mail.mc.pref.osaka.jp
SO Journal of Immunology, (15 Feb 2001) 166/4 (2610-2616).
Refs: 57
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB M161Ag is a 43-kDa surface lipoprotein of Mycoplasma fermentans, serving as a potent cytokine inducer for monocytes/macrophages, maturing dendritic cells (DCs), and activating host complement on affected cells. It possesses a unique N-terminal lipoamino acid, S-diacylglyceryl cysteine. The 2-kDa macrophage-activating lipopeptide-2 (MALP-2), recently identified as a ligand for Toll-like receptor 2 (TLR2), is derived from M161Ag. In this study, we identified structural motifs sustaining the functions of M161Ag using wild-type and unlipidated rM161Ag with (SP(+)) or without signal peptides (SP(-)). Because the SP(+) rM161Ag formed dimers via 25Cys, we obtained a monomeric form by mutagenesis (SP(+)C25S). Only wild type accelerated maturation of human DCs as determined by the CD83/86 criteria, suggesting the importance of the N-terminal fatty acids for this function. Wild-type and the SP(+) form of monomer induced secretion of TNF-.alpha. and IL-12 p40 by human monocytes and DCs. Either lipid or signal peptide at the N-terminal portion of monomer was required for expression of this function. In contrast, murine macrophages produced TNF-.alpha. in response to wild type, but not to any recombinant form of M161Ag, suggesting the species-dependent response to rM161Ag. Wild-type and both monomeric and dimeric SP(+) forms possessed the ability to activate complement via the alternative pathway. Again, the hydrophobic portion was associated with this function. These results, together with the finding that macrophages from ***TLR2*** - ***deficient*** mice did not produce TNF-.alpha. in response to M161Ag, infer that the N-terminal hydrophobic structure of M161Ag is important for TLR2-mediated cell activation and complement activation.

L8 ANSWER 25 OF 28 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2000264814 EMBASE
TI Expression of toll-like receptor 2 on .gamma..delta. T cells bearing invariant V.gamma.6/V.delta.1 induced by Escherichia coli infection in mice.
AU Mokuno Y.; Matsuguchi T.; Takano M.; Nishimura H.; Washizu J.; Ogawa T.; Takeuchi O.; Akira S.; Nimura Y.; Yoshikai Y.
CS Dr. T. Matsuguchi, Lab. of Host Defense/Germfree Life, Res. Inst. for Dis. Mechanism/Ctrl., Nagoya University School of Medicine, 65 Tsurumai-cho Showa-ku, Nagoya 466-8550, Japan. tmatsugu@med.nagoya-u.ac.jp
SO Journal of Immunology, (15 Jul 2000) 165/2 (931-940).
Refs: 56
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB We recently reported that the number of .gamma..delta. T cells was increased after infection with Escherichia coli in C3H/HeN mice. We here showed that an i.p. injection with native lipid A derived from E. coli induced an increase of .gamma..delta. T cells in the peritoneal cavity of LPS-responsive C3H/HeN mice and, albeit to a lesser degree, also in LPS-hyporesponsive C3H/HeJ mice. The purified .gamma..delta. T cells from C3H/HeN and C3H/HeJ mice expressed a canonical TCR repertoire encoded by V.gamma.6-J.gamma.1/V.delta.1-D.delta.2-J.delta.2 gene segments and proliferated in response to the native lipid A derived from E. coli in a TCR-independent manner. The lipid A-reactive .gamma..delta. T cells bearing canonical V.gamma.6/V.delta.1 expressed Toll-like receptor (TLR) 2 mRNA, while TLR4 mRNA was undetectable. Treatment with a TLR2 anti-sense oligonucleotide resulted in hyporesponsiveness of the .gamma..delta. T cells to the native lipid A. ***TLR2*** - ***deficient*** mice showed an impaired increase of the .gamma..delta. T cells following injection of native lipid A. These results suggest that TLR2 is involved in the activation of canonical V.gamma.6/V.delta.1 T cells by native E. coli lipid A.

L8 ANSWER 26 OF 28 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1999245979 EMBASE
TI Signaling events induced by lipopolysaccharide-activated Toll-like receptor 2.
AU Yang R.-B.; Mark M.R.; Gurney A.L.; Godowski P.J.
CS Dr. P.J. Godowski, Department of Molecular Biology, Genentech, Inc., South San Francisco, CA 94080-4990, United States. ski@gene.com
SO Journal of Immunology, (15 Jul 1999) 163/2 (639-643).
Refs: 35
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB Human Toll-like receptor 2 (TLR2) is a signaling receptor that responds to LPS and activates NF-.kappa.B. Here, we investigate further the events triggered by TLR2 in response to LPS. We show that TLR2 associates with the high-affinity LPS binding protein membrane CD14 to serve as an LPS receptor complex, and that LPS treatment enhances the oligomerization of TLR2. Concomitant with receptor oligomerization, the IL-1R-associated kinase (IRAK) is recruited to the ***TLR2*** complex. Intracellular ***deletion*** variants of ***TLR2*** lacking C-terminal 13 or 141

aa fail to recruit IRAK, which is consistent with the inability of these mutants to transmit LPS cellular signaling. Moreover, both deletion mutants could still form complexes with wild-type TLR2 and act in a dominant-negative (DN) fashion to block TLR2-mediated signal transduction. DN constructs of myeloid differentiation protein, IRAK, TNF receptor-associated factor 6, and NF-.kappa.B-inducing kinase, when coexpressed with TLR2, abrogate TLR2-mediated NF-.kappa.B activation. These results reveal a conserved signaling pathway for TLR2 and IL-IRs and suggest a molecular mechanism for the inhibition of TLR2 by DN variants.

L8 ANSWER 27 OF 28 CAPLUS COPYRIGHT 2003 ACS
AN 2000:493319 CAPLUS
DN 133:101728
TI ***TLR2*** and MyD88 gene ***knockout*** mouse as bacterial cell wall component-unresponsive animal model
IN Akira, Shizuo; Takeuchi, Osamu; Takeda, Kiyoshi
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000041561	A1	20000720	WO 2000-JP132	20000113
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1142472	A1	20011010	EP 2000-900372	20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI JP 1999-7365 A 19990114
JP 1999-228282 A 19990812
JP 1999-309238 A 19991029
WO 2000-JP132 W 20000113

AB A ***TLR2*** and MyD88 gene ***knockout*** mouse unresponsive to bacterial cell wall components such as peptidoglycans, lipoproteins, lipopeptides, endotoxin, lipoteichoic acid (LTA) Mycobacterium tuberculosis lysate, etc., useful in clarifying the role of each member of the TLR family (in particular, TLR2 and MyD88) in the signal transduction due to stimulation with bacterial cell components in vivo, is disclosed. This knockout mouse is prepd. by the homologous recombination method with the use of a targeting vector constructed by substituting the whole gene fragment or a part thereof of the exon site contg. the intracellular region of TLR2 or MyD88 gene by a plasmid having poly(A) signal and a marker gene. Also claimed is a screening method for bacterial component responsiveness regulators based on measuring the activation of macrophage or spleen cells, macrophage cytokine or nitrous acid ion prodn., or spleen cell MHC class II expression. More specifically, TLR2 (ant)agonists, interleukin-1 regulators, interleukin-18 regulators, or IFN-.gamma. regulators, or TNF-.alpha. regulators are screened. Lipoproteins/lipopeptides are derived from mycoplasma, Spirochaeta, or Escherichia genus.

RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 28 OF 28 CAPLUS COPYRIGHT 2003 ACS
AN 1999:286079 CAPLUS
DN 130:294563
TI New human homologs of the Drosophila Toll gene
IN Goddard, Audrey; Godowski, Paul J.; Gurney, Austin L.; Mark, Melanie R.; Yang, Ruey-Bing
PA Genentech, Inc., USA
SO PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 104

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9920756	A2	19990429	WO 1998-US21141	19981007
WO 9920756	A3	19990910		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2305385	AA	19990429	CA 1998-2305385	19981007
AU 9910703	A1	19990510	AU 1999-10703	19981007
ZA 9809147	A	20000407	ZA 1998-9147	19981007
EP 1025227	A2	20000809	EP 1998-953294	19981007
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 2002086368	A1	20020704	US 1998-168978	19981007
JP 2002526028	T2	20020820	JP 2000-517077	19981007
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US 2002132252	A1	20020919	US 2001-990442	20011114
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US 2002193299	A1	20021219	US 2001-989735	20011119
US 2003003531	A1	20030102	US 2001-989734	20011119
US 2002103125	A1	20020801	US 2001-989731	20011120
US 2002177164	A1	20021128	US 2001-989293	20011120
US 2002197674	A1	20021226	US 2001-989730	20011120
US 2003004311	A1	20030102	US 2001-28072	20011219
US 2002127584	A1	20020912	US 2002-52586	20020115
WO 2002101069	A2	20021219	WO 2002-US10513	20020403
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				

PRAI US 1997-62250P P 19971017
US 1997-65311P P 19971113
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US 1998-88824P P 19980610
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US 1998-89440P P 19980616
US 1998-89512P P 19980616
WO 1998-US21141 W 19981007
US 2001-880457 A 20010612
US 2001-941992 A1 20010828

AB Three new human homologs of the Drosophila Toll gene are identified and the gene products characterized. CDNAs encoding the human Toll proteins PRO285, PRO286, and PRO358, are cloned for manuf. of the proteins. At least one of the proteins is involved in signal transduction and plays a role in the lipopolysaccharide induction of interleukin 8. The protein may therefore be a target for the treatment or prophylaxis of septic shock. The genes were first identified by screening a com. human EST database for homologs of the Toll protein and the EST sequence used to design primers and probes to identify the gene.

=> d his

(FILE 'HOME' ENTERED AT 15:06:21 ON 06 JAN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:06:35 ON 06 JAN 2003
L1 1254 S TLR4
L2 772 S TLR2
L3 539 S MYD88
L4 105 S L1 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR D
L5 50 DUP REM L4 (55 DUPLICATES REMOVED)
L6 87 S L2 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR D
L7 39 DUP REM L6 (48 DUPLICATES REMOVED)
L8 28 S L7 NOT L5

=> s l3 (3a) (knockout or knock out or deficien? or transgen? or delet?)
L9 90 L3 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR
DELET?)

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PROCESSING COMPLETED FOR L9
L10 40 DUP REM L9 (50 DUPLICATES REMOVED)

=> s l10 not l8
L11 34 L10 NOT L8

=> s l11 not l5
L12 20 L11 NOT L5

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YOU HAVE REQUESTED DATA FROM 20 ANSWERS - CONTINUE? Y/(N):y

L12 ANSWER 1 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2003:366 BIOSIS
DN PREV200300000366
TI Essential role for TIRAP in activation of the signalling cascade shared by TLR2 and TLR4.
AU Yamamoto, Masahiro; Sato, Shintaro; Hemmi, Hiroaki; Sanjo, Hideki; Uematsu, Satoshi; Kaisho, Tsuneyasu; Hoshino, Katsuaki; Takeuchi, Osamu; Kobayashi, Masaya; Fujita, Takashi; Takeda, Kiyoshi; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871, Japan: sakira@biken.osaka-u.ac.jp Japan
SO Nature (London), (21 November 2002) Vol. 420, No. 6913, pp. 324-329. print.
ISSN: 0028-0836.
DT Article; Letter
LA English
AB Signal transduction through Toll-like receptors (TLRs) originates from their intracellular Toll/interleukin-1 receptor (TIR) domain, which binds to MyD88, a common adaptor protein containing a TIR domain. Although cytokine production is completely abolished in ***MyD88*** - ***deficient*** mice, some responses to lipopolysaccharide (LPS), including the induction of interferon-inducible genes and the maturation of dendritic cells, are still observed. Another adaptor, TIRAP (also known as Mal), has been cloned as a molecule that specifically associates with TLR4 and thus may be responsible for the MyD88-independent response. Here we report that LPS-induced splenocyte proliferation and cytokine production are abolished in mice lacking TIRAP. As in ***MyD88*** - ***deficient*** mice, LPS activation of the nuclear factor NF-kappaB and mitogen-activated protein kinases is induced with delayed kinetics in TIRAP-deficient mice. Expression of interferon-inducible genes and the maturation of dendritic cells is observed in these mice; they also show defective response to TLR2 ligands, but not to stimuli that activate TLR3, TLR7 or TLR9. In contrast to previous suggestions, our results show that TIRAP is not specific to TLR4 signalling and does not participate in the MyD88-independent pathway. Instead, TIRAP has a crucial role in the MyD88-dependent signalling pathway shared by TLR2 and TLR4.

L12 ANSWER 2 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:561041 BIOSIS
DN PREV200200561041
TI Critical roles of myeloid differentiation factor 88-dependent proinflammatory cytokine release in early phase clearance of Listeria monocytogenes in mice.
AU Seki, Ekihiro; Tsutsui, Hiroko; Tsuji, Noriko M.; Hayashi, Nobuki; Adachi, Keishi; Nakano, Hiroki; Futatsugi-Yumikura, Shizue; Takeuchi, Osamu; Hoshino, Katsuaki; Akira, Shizuo; Fujimoto, Jiro; Nakanishi, Kenji (1)
CS (1) Department of Immunology and Medical Zoology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya, 663-8501: nakaken@hyo-med.ac.jp Japan
SO Journal of Immunology, (October 1, 2002) Vol. 169, No. 7, pp. 3863-3868. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Listeria monocytogenes (LM), a facultative intracellular Gram-positive bacterium, often causes lethal infection of the host. In this study we investigated the molecular mechanism underlying LM eradication in the early phase of infection. Upon infection with LM, both IL-12 and IL-18 were produced, and then they synergistically induced IFN-gamma production, leading to normal LM clearance in the host. IFN-gamma knockout (KO) mice were highly susceptible to LM infection. IL-12/IL-18 double knockout mice were also highly susceptible. Their susceptibility was less than that of IFN-gamma KO mice, but more than that of single IL-12 or IL-18 KO mice. Mice deficient in myeloid differentiation factor 88 (MyD88), an essential adaptor molecule used by signal transduction pathways of all members of the Toll-like receptor (TLR) family, showed an inability to produce IL-12 and IFN-gamma following LM infection and were most susceptible to LM. Furthermore, ***MyD88*** - ***deficient*** , but not IFN-gamma-deficient, Kupffer cells could not produce TNF-alpha in response to LM in vitro, indicating the importance of MyD88-dependent TNF-alpha production for host defense. As TLR2 KO, but not TLR4 KO, mice showed partial impairment in their capacity to produce IL-12, IFN-gamma, and TNF-alpha, TLR2 activation partly contributed to the induction of IL-12-mediated IFN-gamma production. These results indicated a critical role for TLRs/MyD88-dependent IL-12/TNF-alpha production and for IL-12- and IL-18-mediated IFN-gamma production in early phase clearance of LM.

L12 ANSWER 3 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:547771 BIOSIS
DN PREV200200547771
TI Caspase-9/-3 activation and apoptosis are induced in mouse macrophages upon ingestion and digestion of Escherichia coli bacteria.
AU Haecker, Hans; Fuermann, Christine; Wagner, Hermann; Haecker, Georg (1)
CS (1) Institute for Medical Microbiology, Immunology, and Hygiene, Technische Universitaet Muenchen, Trogerstrasse 9, D-81675, Munich: hacker@lrz.tum.de Germany
SO Journal of Immunology, (September 15, 2002) Vol. 169, No. 6, pp. 3172-3179. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB A number of highly virulent, intracellular bacteria are known to induce cell death by apoptosis in infected host cells. In this work we

demonstrate that phagocytosis of bacteria from the Escherichia coli laboratory strain K12 DH5alpha is a potent cell death stimulus for mouse macrophages. RAW264.7 mouse macrophages took up bacteria and digested them within 2-4 h as investigated with green fluorescent protein-expressing bacteria. No evidence of apoptosis was seen at 8 h postexposure, but at 24 h apprx70% of macrophages displayed an apoptotic phenotype by a series of parameters. Apoptosis was blocked by inhibition of caspases or by forced expression of the apoptosis-inhibiting protein Bcl-2. Processing of caspase-3 and caspase-9 but not caspase-8 was seen suggesting that the mitochondrial branch of the apoptotic pathway was activated. Active effector caspases could be detected in two different assays. Because the adapter molecule myeloid differentiation factor 88 (MyD88) has been implicated in apoptosis, involvement of the Toll-like receptor pathway was investigated. In RAW264.7 cells, heat-treated bacteria were taken up poorly and failed to induce significant apoptosis. However, cell activation was almost identical between live and heat-inactivated bacteria as measured by extracellular signal-regulated kinase activation, generation of free radicals, and TNF secretion. Furthermore, primary bone marrow-derived macrophages from wild-type as well as from ***MyD88*** - ***deficient*** mice underwent apoptosis upon phagocytosis of bacteria. These results show that uptake and digestion of bacteria leads to MyD88-independent apoptosis in mouse macrophages. This form of cell death might have implications for the generation of the immune response.

L12 ANSWER 4 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:547727 BIOSIS
DN PREV200200547727
TI Cutting edge: Myeloid differentiation factor 88 deficiency improves resistance against sepsis caused by polymicrobial infection.
AU Weighardt, Heike; Kaiser-Moore, Simone; Vabulas, Ramunas M.; Kirschning, Carsten J.; Wagner, Hermann; Holzmann, Bernhard (1)
CS (1) Department of Surgery, Klinikum Rechts der Isar, Technische Universitaet Muenchen, Ismaninger Strasse 22, 81675, Muenchen: holzmann@nt1.chir.med.tu-muenchen.de Germany
SO Journal of Immunology, (September 15, 2002) Vol. 169, No. 6, pp. 2823-2827. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Toll-like receptors (TLRs) are important for the activation of innate immune cells upon encounter of microbial pathogens. The present study investigated the potential roles of TLR2, TLR4, and the signaling protein myeloid differentiation factor 88 (MyD88) in polymicrobial septic peritonitis. Whereas both TLR2 and TLR4 were dispensable for host defense against septic peritonitis, ***MyD88*** - ***deficient*** mice were protected in this infection model. Recruitment of neutrophils to the septic focus and bacterial clearance were normal in ***MyD88*** - ***deficient*** mice. In contrast, the systemic inflammatory response was strongly attenuated in the absence of ***MyD88*** . Surprisingly, ***MyD88*** ***deficiency*** did not alter cytokine and chemokine production in spleen, but markedly reduced the inflammatory response in liver and lung. Production of monocyte chemoattractant protein-1 and macrophage-inflammatory protein-1alpha was entirely independent of MyD88. These results imply a central role of MyD88 for the systemic immune pathology of polymicrobial sepsis and show that cytokine production in spleen and induction of certain chemokines are MyD88 independent.

L12 ANSWER 5 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:517503 BIOSIS
DN PREV200200517503
TI A universal role for MyD88 in TLR/IL-1R-mediated signaling.
AU Janssens, Sophie (1); Beyaert, Rudi (1)
CS (1) Dept of Molecular Biomedical Research, Unit of Molecular Signal Transduction in Inflammation, Ghent University-VIB, K.L. Ledeganckstraat 35, B-9000, Gent: Rudi.Beyaert@dmb.rug.ac.be Belgium
SO Trends in Biochemical Sciences, (September, 2002) Vol. 27, No. 9, pp. 474-482. http://journals.bmn.com/journals/list/latest?jcode=tibs. print.
ISSN: 0968-0004.
DT General Review
LA English
AB The MyD88 adapter protein links members of the toll-like receptor (TLR) and interleukin-1 receptor (IL-1R) superfamily to the downstream activation of nuclear factor-kappaB and mitogen-activated protein kinases. Although originally identified as a myeloid-differentiation marker, MyD88 is now known to play an essential role in the innate immune response of insects and mammals. The generation of ***MyD88*** - ***deficient*** mice, as well as the identification of MyD88-related proteins and regulators of MyD88 signaling, has revealed new and important insights into the function of MyD88.

L12 ANSWER 6 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:449990 BIOSIS
DN PREV200200449990
TI Endotoxin can induce ***MyD88*** - ***deficient*** dendritic cells to support Th2 cell differentiation.
AU Kaisho, Tsuneyasu; Hoshino, Katsuaki; Iwabe, Tomio; Takeuchi, Osamu; Yasui, Teruhito; Akira, Shizuo (1)
CS (1) Department of Host Defense, SORST, Japan Science and Technology Corporation, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO International Immunology, (July, 2002) Vol. 14, No. 7, pp. 695-700. http://www.intimm.oupjournals.org. print.
ISSN: 0953-8178.
DT Article
LA English
AB Toll-like receptor (TLR) signaling activates dendritic cells (DC) to secrete proinflammatory cytokines and up-regulate co-stimulatory molecule expression, thereby linking innate and adaptive immunity. A TLR-associated adapter protein, MyD88, is essential for cytokine production induced by TLR. However, in response to a TLR4 ligand, lipopolysaccharide (LPS), ***MyD88*** - ***deficient*** (***MyD88*** -/-) DC can up-regulate co-stimulatory molecule expression and enhance their T cell stimulatory activity, indicating that the MyD88-independent pathway through TLR4 can induce some features of DC maturation. In this study, we have further characterized function of LPS-stimulated, MyD88-/- DC. In response to LPS, wild-type DC could enhance their ability to induce IFN-gamma production in allogeneic mixed lymphocyte reaction (alloMLR). In contrast, in response to LPS, MyD88-/- DC augmented their ability to induce IL-4 instead of IFN-gamma in alloMLR. Impaired production of Th1-inducing cytokines in MyD88-/- DC cannot fully account for their increased Th2 cell-supporting ability, because absence of Th1-inducing cytokines in DC caused impairment of IFN-gamma, but did not lead to augmentation of IL-4 production in alloMLR. In vivo experiments with adjuvants also revealed Th2-skewed immune responses in MyD88-/- mice. These results demonstrate that the MyD88-independent pathway through TLR4 can confer on DC the ability to support Th2 immune responses.

L12 ANSWER 7 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:359075 BIOSIS
DN PREV200200359075
TI Lipopolysaccharide-dependent prostaglandin E2 production is regulated by the glutathione-dependent prostaglandin E2 synthase gene induced by the toll-like receptor 4/MyD88/NF-IL6 pathway.
AU Uematsu, Satoshi; Matsumoto, Makoto; Takeda, Kiyoshi; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO Journal of Immunology, (June 1, 2002) Vol. 168, No. 11, pp. 5811-5816. http://www.jimmunol.org/. print.
ISSN: 0022-1767.
DT Article
LA English
AB Macrophages produce a large amount of PGE2 during inflammation. This lipid mediator modulates various immune responses. PGE2 acts on macrophages and inhibits production of cytokines such as TNF-alpha and IL-12. Membrane-bound glutathione-dependent PGE2 synthase (mPGES) has been shown to be a terminal enzyme of the cyclooxygenase-2-mediated PGE2 biosynthesis. Here we identified mPGES as a molecule that is induced by LPS in macrophages. The expression of mPGES was not induced by LPS in mice lacking Toll-like receptor 4 or ***MyD88*** . Furthermore, mice ***deficient*** in NF-IL6 showed neither induction of mPGES nor biosynthesis of PGE2 in response to LPS, indicating that mPGES expression in response to LPS is regulated by a Toll-like receptor 4/MyD88/NF-IL6-dependent signaling pathway. We generated mPGES-deficient mice and investigated the role of mPGES in vivo. The mice showed no augmentation of the PGE2 production in response to LPS. However, they were not impaired in the LPS-induced production of inflammatory cytokines and showed normal response to the LPS-induced shock. Thus, mPGES is critically involved in the biosynthesis of PGE2 induced by LPS, but is dispensable for the modulation of inflammatory responses.

L12 ANSWER 8 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:315520 BIOSIS
DN PREV200200315520
TI HSP70 as endogenous stimulus of the Toll/interleukin-1 receptor signal pathway.
AU Vabulas, Ramunas M.; Ahmad-Nejad, Parviz; Ghose, Sanghamitra; Kirschning, Carsten J.; Issels, Rolf D.; Wagner, Hermann (1)
CS (1) Institute of Medical Microbiology, Immunology and Hygiene, Technical University of Munich, Trogerstrasse 9, Munich, 81675: h.wagner@lrz.tu-muenchen.de Germany
SO Journal of Biological Chemistry, (April 26, 2002) Vol. 277, No. 17, pp. 15107-15112. http://www.jbc.org/. print.
ISSN: 0021-9258.
DT Article
LA English
AB Human heat-shock protein (HSP)70 activates innate immune cells and hence requires no additional adjuvants to render bound peptides immunogenic. Here we tested the assumption that endogenous HSP70 activates the Toll/IL-1 receptor signal pathway similar to HSP60 and pathogen-derived molecular patterns. We show that HSP70 induces interleukin-12 (IL-12) and endothelial cell-leukocyte adhesion molecule-1 (ELAM-1) promoters in macrophages and that this is controlled by MyD88 and TRAF6. Furthermore, HSP70 causes ***MyD88*** relocalization and ***MyD88*** - ***deficient*** dendritic cells do not respond to HSP70 with proinflammatory cytokine production. Using the system of genetic complementation with Toll-like receptors (TLR) we found that TLR2 and TLR4

confer responsiveness to HSP70 in 293T fibroblasts. The expanding list of endogenous ligands able to activate the ancient Toll/IL-1 receptor signal pathway is in line with the "danger hypothesis" proposing that the innate immune system senses danger signals even if they originate from self.

L12 ANSWER 9 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:241903 BIOSIS
DN PREV200200241903
TI In the absence of IL-12, CD4+ T cell responses to intracellular pathogens fail to default to a Th2 pattern and are host protective in an IL-10-/- setting.
AU Jankovic, Dragana (1); Kullberg, Marika C.; Hieny, Sara; Caspar, Patricia; Collazo, Carmen M.; Sher, Alan
CS (1) Laboratory of Parasitic Diseases, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD, 20892: djankovic@niaid.nih.gov USA
SO Immunity, (March, 2002) Vol. 16, No. 3, pp. 429-439. http://www.immunity.com/. print.
ISSN: 1074-7613.
DT Article
LA English
AB IL-12-deficient mice exposed to nonlethal infections with intracellular pathogens or repeatedly immunized with a pathogen extract developed lowered but nevertheless substantial numbers of IFN-gamma+ CD4+ T cells compared to those observed in wild-type animals. Moreover, the CD4+ responses in these knockout animals failed to default to a Th2 pattern. The protective efficacy of the Th1 cells developing in an IL-12-deficient setting was found to be limited by IL-10 since mice doubly deficient in IL-10 and IL-12 survived, while animals deficient in IL-12 alone succumbed to pathogen challenge. In contrast to IL-12 ***knockout** mice, ***MyD88*** - ***deficient*** animals exposed to a Th1 microbial stimulus developed a pure Th2 response, arguing that this signaling element plays a more critical function than IL-12 in determining pathogen-induced CD4 polarization.

L12 ANSWER 10 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:372799 BIOSIS
DN PREV200100372799
TI Dendritic-cell function in toll-like receptor- and ***MyD88*** - ***knockout*** mice.
AU Kaisho, Tsuneyasu (1); Akira, Shizuo
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Yamadaoka 3-1, Suita, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO Trends in Immunology, (February, 2001) Vol. 22, No. 2, pp. 78-83. print.
ISSN: 1471-4906.
DT General Review
LA English
SL English

L12 ANSWER 11 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:219024 BIOSIS
DN PREV200100219024
TI The role of Toll-like receptors and MyD88 in innate immune responses.
AU Akira, Shizuo (1); Hoshino, Katsuaki; Kaisho, Tsuneyasu
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871: sakira@biken.osaka-u.ac.jp Japan
SO Journal of Endotoxin Research, (2000) Vol. 6, No. 5, pp. 383-387. print.
ISSN: 0968-0519.
DT Article
LA English
SL English
AB Toll-like receptors (TLRs) are phylogenetically conserved receptors that recognize pathogen associated molecular patterns (PAMPS). We previously generated mice lacking TLR2 and TLR4 and showed the differential role of TLR2 and TLR4 in microbial recognition. TLR4 functions as the transmembrane component of the lipopolysaccharide (LPS) receptor, while TLR2 recognizes peptidoglycan from Gram-positive bacteria and lipoprotein. We also generated mice lacking MyD88, an adaptor involved in IL-1R/TLR signalings. The responses to a variety of bacterial components were completely abrogated in ***MyD88*** - ***deficient*** cells. However, unlike the signaling mediated by other bacterial components such as lipoprotein and bacterial DNA, activation of NF-kappaB and MAP kinases was induced in response to LPS even in the absence of MyD88, which indicates the existence of a MyD88-independent pathway. We have recently found that the MyD88-independent pathway is involved in LPS-induced maturation of dendritic cells (DCs).

L12 ANSWER 12 OF 20 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:378552 BIOSIS
DN PREV199900378552
TI Unresponsiveness of ***MyD88*** - ***deficient*** mice to endotoxin.
AU Kawai, Taro; Adachi, Osamu; Ogawa, Tomohiko; Takeda, Kiyoshi; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871 Japan
SO Immunity, (July, 1999) Vol. 11, No. 1, pp. 115-122.
ISSN: 1074-7613.
DT Article
LA English
SL English
AB MyD88 is a general adaptor protein that plays an important role in the Toll/IL-1 receptor family signalings. Recently, Toll-like receptors 2 and 4 (TLR2 and TLR4) have been suggested to be the signaling receptors for lipopolysaccharide (LPS). In this study, we demonstrate that ***MyD88*** ***knockout*** mice lack the ability to respond to LPS as measured by shock response, B cell proliferative response, and secretion of cytokines by macrophages and embryonic fibroblasts. However, activation of neither NF-kappaB nor the mitogen-activated protein (MAP) kinase family is abolished in ***MyD88*** ***knockout*** mice. These findings demonstrate that signaling via MyD88 is essential for LPS response, but the inability of ***MyD88*** ***knockout*** mice to induce LPS-dependent gene expression cannot simply be attributed to lack of the activation of MAP kinases and NF-kappaB.

L12 ANSWER 13 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002450639 EMBASE
TI MyD88 as a bottle neck in Toll/IL-1 signaling.
AU Takeuchi O.; Akira S.
CS O. Takeuchi, Department of Host Defense, Research Inst. for Microbial Dis., Osaka University, 3-1 Yamadaoka, Suita, Osaka 565-0871, Japan. otaake@biken.osaka-u.ac.jp
SO Current Topics in Microbiology and Immunology, (2002) 270/- (155-167).
Refs: 64
ISSN: 0070-217X CODEN: CTMIA3
CY Germany
DT Journal; General Review
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Myeloid differentiation factor 88 (MyD88) is an adaptor molecule composed of an N-terminal death domain and a C-terminal Toll/interleukin (IL)-1R homology domain. Ligand binding to Toll-like receptor (TLR)/IL-1R family members results in the association of MyD88 to the cytoplasmic tail of receptors; this then initiates the signaling cascade that leads to the activation of nuclear factor-.kappa.B and mitogen-activated protein kinases. Analysis of ***MyD88*** - ***deficient*** mice revealed its essential role in TLR/IL-1R signaling as well as in both the innate and the adaptive immune response.

L12 ANSWER 14 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002062327 EMBASE
TI Small-antiviral compounds activate immune cells via the TLR7 MyD88-dependent signaling pathway.
AU Hemmi H.; Kaisho T.; Takeuchi O.; Sato S.; Sanjo H.; Hoshino K.; Horiuchi T.; Tomizawa H.; Takeda K.; Akira S.
CS S. Akira, Department of Host Defense, Researh Inst. for Microbial Diseases, Osaka Univ./Solution-oriented Res., 3-1 Yamada-oka, Suita, Osaka 565-0871, Japan. sakira@biken.osaka-u.ac.jp
SO Nature Immunology, (2002) 3/2 (196-200).
Refs: 49
ISSN: 1529-2908 CODEN: NIAMCZ
CY United States
DT Journal; Article
FS 004 Microbiology
016 Cancer
026 Immunology, Serology and Transplantation
030 Pharmacology
037 Drug Literature Index
LA English
SL English
AB The imidazoquinoline compounds imiquimod and R-848 are low-molecular-weight immune response modifiers that can induce the synthesis of interferon-.alpha. and other cytokines in a variety of cell types. These compounds have potent anti-viral anti-tumor properties; however, the mechanisms by which they exert their anti-viral activities remain unclear. Here we show that the imidazoquinolines activate immune cells via the Toll-like receptor 7 (TLR7)-MyD88-dependent signaling pathway. In response to the imidazoquinolines, neither ***MyD88*** - nor TLR7- ***deficient*** mice showed any inflammatory cytokine production by macrophages, proliferation of splenocytes or maturation of dendritic cells. Imidazoquinoline-induced signaling events were also abolished in both ***MyD88*** - and TLR7- ***deficient*** mice.

L12 ANSWER 15 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2002027416 EMBASE
TI Drosophila MyD88 is required for the response to fungal and Gram-positive bacterial infections.
AU Tauszig-Delamasure S.; Bilak H.; Capovilla M.; Hoffmann J.A.; Imler J.-L.
CS J.-L. Imler, UPR9022 du Ctr Natl. Recherche Sci., Inst. de Biol. Moleculaire et Cell., 15 rue Rene Descartes, 67000 Strasbourg, France. JLImler@ibmc.u-strasbg.fr
SO Nature Immunology, (2002) 3/1 (91-97).
Refs: 50
ISSN: 1529-2908 CODEN: NIAMCZ
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English

SL English
AB We report here the identification and functional characterization of DmMyD88, a gene encoding the Drosophila homolog of mammalian MyD88. DmMyD88 combines a Toll-IL-1R homology (TIR) domain and a death domain. Overexpression of DmMyD88 was sufficient to induce expression of the antifungal peptide Drosomycin, and induction of Drosomycin was markedly reduced in DmMyD88-mutant flies. DmMyD88 interacted with Toll through its TIR domain and required the death domain proteins Tube and Pelle to activate expression of Drs, which encodes Drosomycin. DmMyD88-mutant flies were highly susceptible to infection by fungi and Gram-positive bacteria, but resisted Gram-negative bacterial infection much as did wild-type flies. Phenotypic comparison of DmMyD88-mutant flies and ***MyD88*** - ***deficient*** mice showed essential differences in the control of Gram-negative infection in insects and mammals.

L12 ANSWER 16 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001369459 EMBASE
TI Toll-like receptors control activation of adaptive immune responses.
AU Schnare M.; Barton G.M.; Holt A.C.; Takeda K.; Akira S.; Medzhitov R.
CS R. Medzhitov, Section of Immunobiology, Yale University School of Medicine, Howard Hughes Medical Institute, New Haven, CT 06520, United States. ruslan@yale.edu
SO Nature Immunology, (2001) 2/10 (947-950).
Refs: 23
ISSN: 1529-2908 CODEN: NIAMCZ
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
029 Clinical Biochemistry
LA English
SL English
AB Mechanisms that control the activation of antigen-specific immune responses in vivo are poorly understood. It has been suggested that the initiation of adaptive immune responses is controlled by innate immune recognition. Mammalian Toll-like receptors play an essential role in innate immunity by recognizing conserved pathogen-associated molecular patterns and initiating the activation of NF-.kappa.B and other signaling pathways through the adapter protein, MyD88. Here we show that ***MyD88*** - ***deficient*** mice have a profound defect in the activation of antigen-specific T helper type I (T(H)1) but not T(H)2 immune responses. These results suggest that distinct pathways of the innate immune system control activation of the two effector arms of adaptive immunity.

L12 ANSWER 17 OF 20 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 2001078899 EMBASE
TI Lipopolysaccharide-induced IL-18 secretion from murine Kupffer cells independently of myeloid differentiation factor 88 that is critically involved in induction of production of IL-12 and IL-1.beta..
AU Seki E.; Tsutsui H.; Nakano H.; Tsuji N.M.; Hoshino K.; Adachi O.; Adachi K.; Futatsugi S.; Kuida K.; Takeuchi O.; Okamura H.; Fujimoto J.; Akira S.; Nakanishi K.
CS Dr. K. Nakanishi, Dept. of Immunology/Medical Zoology, Hyogo College of Medicine, 1-1 Mukogawa-cho, Nishinomiya 663-8501, Japan. nakaken@hyo-med.ac.jp
SO Journal of Immunology, (15 Feb 2001) 166/4 (2651-2657).
Refs: 43
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 026 Immunology, Serology and Transplantation
LA English
SL English
AB IL-18, produced as biologically inactive precursor, is secreted from LPS-stimulated macrophages after cleavage by caspase-1. In this study, we investigated the mechanism underlying caspase-1-mediated IL-18 secretion. Kupffer cells constantly stored IL-18 and constitutively expressed caspase-1. Inhibition of new protein synthesis only slightly reduced IL-18 secretion, while it decreased and abrogated their IL-1.beta. and IL-12 secretion, respectively. Kupffer cells deficient in Toll-like receptor (TLR) 4, an LPS-signaling receptor, did not secrete IL-18, IL-1.beta., and IL-12 upon LPS stimulation. In contrast, Kupffer cells lacking myeloid differentiation factor 88 (MyD88), an adaptor molecule for TLR-mediated-signaling, secreted IL-18 without IL-1.beta. and IL-12 production in a caspase-1-dependent and de novo synthesis-independent manner. These results indicate that MyD88 is essential for IL-12 and IL-1.beta. production from Kupffer cells while their IL-18 secretion is mediated via activation of endogenous caspase-1 without de novo protein synthesis in a MyD88-independent fashion after stimulation with LPS. In addition, infection with Listeria monocytogenes, products of which have the capacity to activate TLR, increased serum levels of IL-18 in wild-type and ***MyD88*** - ***deficient*** mice but not in caspase-1-deficient mice, whereas it induced elevation of serum levels of IL-12 in both wild-type and caspase-1-deficient mice but not in ***MyD88*** - ***deficient*** mice. Taken together, these results suggested caspase-1-dependent, MyD88-independent IL-18 release in bacterial infection.

L12 ANSWER 18 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2002:116477 CAPLUS
DN 137:183888
TI Critical roles of an adaptor protein, MyD88, in signal transduction through toll-like receptors
AU Kaisho, Tsuneyasu; Akira, Shizuo
CS Department of Host Defense, Research Institute for Mecrobial Diseases, Osaka University, Japan
SO Jikken Igaku (2001), 19(18), 2370-2375
CODEN: JIIGEF; ISSN: 0288-5514
PB Yodosha
DT Journal; General Review
LA Japanese
AB A review discusses role of MyD88 in signal transduction of toll-like receptors expressed on the surface of macrophages and dendritic cells by using ***MyD88*** ***knock*** ***out*** mouse model.

L12 ANSWER 19 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 2000:818746 CAPLUS
DN 134:99254
TI Toll-like receptors: lessons from knockout mice
AU Akira, S.
CS Dep. Host Defense, Osaka Univ., Suita, 565-0871, Japan
SO Biochemical Society Transactions (2000), 28(5), 551-556
CODEN: BCSTB5; ISSN: 0300-5127
PB Portland Press Ltd.
DT Journal; General Review
LA English
AB A review with 48 refs. To Toll signaling pathway, which is required for establishment of dorsoventral polarity in Drosophila embryos, plays an important role in the response to microbial infections. Recently, Toll-like receptors (TLRs) have also been identified in mammals. TLR4 has been shown to function as the transmembrane component of the lipopolysaccharide receptor, while TLR2 recognizes peptidoglycans from Gram-pos. bacteria, lipoproteins and yeast. Although various microbial cell-wall components are recognized by different receptors, all of these responses are abrogated in ***MyD88*** - ***deficient*** cells. These results show that different TLRs recognize different microbial cell-wall components, and that MyD88 is an essential signaling mol. shared among interleukin-1 receptor/Toll family members.
RE.CNT 48 THERE ARE 48 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L12 ANSWER 20 OF 20 CAPLUS COPYRIGHT 2003 ACS
AN 1999:516118 CAPLUS
DN 132:193028
TI Toll-like receptors and lipopolysaccharide signal transduction
AU Akira, Shizuo
CS Res. Inst. Microb. Dis., Osaka Univ., Japan
SO Molecular Medicine (Tokyo) (1999), 36(Rinji Zokango, Men'eki 1999-2000), 76-83
CODEN: MOLMEL; ISSN: 0918-6557
PB Nakayama Shoten
DT Journal; General Review
LA Japanese
AB A review with 24 refs. Drosophila uses different Toll family members for induction of anti-bacterium and anti-fungus peptide; Toll for anti-fungal drosomycin through Dorsal and 18 Wheeler for anti-bacterial peptides such as cecropin and attain through Dif. Humans possess Toll-like receptors (TLR) and use them for immunity. TLR family members use components in the signal transaction of interleukin 1 (IL-1) including NF.kappa.B. TLR2 and TLR4 are hypothesized to be a lipopolysaccharide (LPS) binding receptor and a receptor participating in LPS signal transduction, resp. MyD88 (myeloid differentiation primary response) is homologous to Toll and expressed specifically in myeloid lineage. MyD88 is prerequisite for in IL-1 and IL-18 signal transduction. ***MyD88*** ***knock*** ***out*** mouse survives upon high dose i.p. administration of LPS, being different from dying wild mouse. LPS signal transduction is hypothesized: binding of LPS with LPS binding protein (LBP), binding of LPS/LBP complex with CD14, and binding of LPS to TLR2/TLR4 receptor followed by MyD88 mediation of signal transduction.

=> s (mouse or mice) and (unresponsive or nonresponsive) and bacteri?
L13 460 (MOUSE OR MICE) AND (UNRESPONSIVE OR NONRESPONSIVE) AND BACTERI?

=> dup rem l13
PROCESSING COMPLETED FOR L13
L14 263 DUP REM L13 (197 DUPLICATES REMOVED)

=> s l14 and (lipoteichoic acid or endotoxin or mycobacterium tuberculosis or peptidoglycan)
L15 52 L14 AND (LIPOTEICHOIC ACID OR ENDOTOXIN OR MYCOBACTERIUM TUBERCU
LOSIS OR PEPTIDOGLYCAN)

=> s l15 and py<1999
2 FILES SEARCHED...
L16 39 L15 AND PY<1999

=> d his

(FILE 'HOME' ENTERED AT 15:06:21 ON 06 JAN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 15:06:35 ON 06 JAN 2003
L1 1254 S TLR4

L2 772 S TLR2
L3 539 S MYD88
L4 105 S L1 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR D
L5 50 DUP REM L4 (55 DUPLICATES REMOVED)
L6 87 S L2 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR D
L7 39 DUP REM L6 (48 DUPLICATES REMOVED)
L8 28 S L7 NOT L5
L9 90 S L3 (3A) (KNOCKOUT OR KNOCK OUT OR DEFICIEN? OR TRANSGEN? OR
L10 40 DUP REM L9 (50 DUPLICATES REMOVED)
L11 34 S L10 NOT L8
L12 20 S L11 NOT L5
L13 460 S (MOUSE OR MICE) AND (UNRESPONSIVE OR NONRESPONSIVE) AND BACTE
L14 263 DUP REM L13 (197 DUPLICATES REMOVED)
L15 52 S L14 AND (LIPOTEICHOIC ACID OR ENDOTOXIN OR MYCOBACTERIUM TUBE
L16 39 S L15 AND PY<1999

=> s l16 not l5
L17 39 L16 NOT L5

=> s l16 not l8
L18 39 L16 NOT L8

=> s l16 not l12
L19 39 L16 NOT L12

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 39 ANSWERS - CONTINUE? Y/(N):y

L19 ANSWER 1 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:225812 BIOSIS
DN PREV199800225812
TI Sexual dimorphism in the ***mouse*** hypothalamic-pituitary-adrenal axis function after ***endotoxin*** and insulin stresses during development.
AU Spinedi, Eduardo (1); Chisari, Andrea; Pralong, Francois; Gaillard, Rolf C.
CS (1) IMBICE, Calle 526e/10 y 11, cc 403, 1900 La Plata Argentina
SO Neuroimmunomodulation, (***March-April, 1997***) Vol. 4, No. 2, pp. 77-83.
ISSN: 1021-7401.
DT Article
LA English
AB Bidirectional communication between the immune and the endocrine systems is now widely accepted as essential for the survival of the organism. Since a classical ***nonresponsive*** period of the hypothalamic-pituitary-adrenal (HPA) axis takes place shortly after birth and because endogenous sex hormones modulate immune function, the aim of the present work was to determine whether sex steroids regulate the PHA axis response to immune (***bacterial*** , lipopolysaccharide, LPS) and nonimmune (insulin, INS) stressors in ***mice*** during development. For this purpose 7-, 15-, 30-, 45- and 60-day-old ***mice*** of both sexes were intraperitoneally injected with either vehicle alone (basal) or containing LPS (2 mg/kg body weight) or INS (12 IU/kg body weight). The animals were then killed by decapitation, 2 h or 45 min after LPS or INS, respectively. Plasma samples were assayed to measure corticosterone concentrations. The results indicated that: (a) there was a transient increase in basal plasma corticosterone levels during development, with a peak value at the juvenile age, regardless of sex; (b) a higher basal plasma corticosterone concentration in females than in males characterized the adult age; (c) the infantile age is a period of the HPA axis function ***nonresponsive*** to purely neuroendocrine but not to inflammatory stimuli; (d) during the juvenile age, females showed a hyporesponsive HPA axis to neuroendocrine and immune stress, whereas male ***mice*** were fully ***unresponsive*** to both challenges; (e) animals of both sexes showed a maximal HPA axis response to purely neuroendocrine stress at the prepubertal age; this response to the immune stimulus was also maximal in 30-day-old males, while it was found in females after puberty (45-day-old ***mice***); (f) sexual dimorphism in the HPA axis response to a purely neuroendocrine stimulus was found at 30 days of age or later, while this characteristic of the response to ***endotoxin*** was not present until puberty. These data clearly suggest that these are gender-dependent characteristics of the ontogeny of the HPA and HP-gonadal axes that are responsible for the sexual dimorphism of HPA axis function in ***mice*** .

L19 ANSWER 2 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1997:393521 BIOSIS
DN PREV199799692724
TI The ***endotoxin*** of Helicobacter pylori is a modulator of host-dependent gastritis.
AU Sakagami, Takashi; Vella, Jennifer; Dixon, Michael F.; O'Rourke, Jani; Radcliff, Fiona; Sutton, Philip; Shimoyama, Takashi; Beagley, Ken; Lee, Adrian (1)
CS (1) Sch. Microbiol. Immunol., Univ. New South Wales, Sydney 2052 Australia
SO Infection and Immunity, (1997) Vol. 65, No. 8, pp. 3310-3316.
ISSN: 0019-9567.
DT Article
LA English
AB Atrophic gastritis caused by Helicobacter pylori is the precursor lesion in the development of intestinal-type gastric adenocarcinoma. In animal models, atrophic gastritis induced by Helicobacter felis has been shown to be host dependent, developing in some ***mouse*** strains and not in others. The lipopolysaccharide (LPS) of H. pylori has been suggested to play a role in the induction of gastritis. The goal of this study was to compare the inflammation induced by long-term infection of the C3H/He and the C3H/HeJ strains of ***mice*** with H. felis. C3H/HeJ ***mice*** are ***unresponsive*** to LPS. Six months after infection, severe atrophic gastritis had developed in the body mucosae of all infected C3H/He ***mice*** , with replacement of parietal and chief cells. Atrophy was associated with a loss of the H. felis from the antral mucosa. In contrast, no atrophy was seen in the infected C3H/HeJ non-LPS responder animals, and heavy colonization of the antrum remained. There were no significant differences between both the quantitative and qualitative serum immunoglobulin G (IgG) and salivary IgA levels in both strains of ***mice*** . The main difference between the two strains of long-term-infected ***mice*** was a lack of macrophage infiltration in the lamina propria. Immunization induced good protective immunity to challenge with viable H. felis. Helicobacter-induced, host-dependent gastritis is likely to be cell mediated. The C3H/He and C3H/HeJ ***mouse*** model provides an excellent opportunity to investigate the cellular basis of atrophic gastritis.

L19 ANSWER 3 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1996:510494 BIOSIS
DN PREV199699232850
TI CD14 is a cell-activating receptor for ***bacterial*** ***peptidoglycan*** .
AU Gupta, Dipika,; Kirkland, Theo N.; Viriyakosol, Suganya; Dziarski, Roman (1)
CS (1) Northwest Cent. Med. Educ., Indiana Univ. Sch. Med., 3400 Broadway, Gary, IN 46408 USA
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 38, pp. 23310-23316.
ISSN: 0021-9258.
DT Article
LA English
AB The hypothesis that CD14 (an ***endotoxin*** receptor present on macrophages and neutrophils) acts as a cell-activating receptor for ***bacterial*** ***peptidoglycan*** was tested using ***mouse*** 70Z/3 cells transfected with human CD14. 70Z/3 cells transfected with an empty vector were ***unresponsive*** to insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of ***endotoxin*** . 70Z/3-CD14 cells were responsive to both insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of ***endotoxin*** , as measured by the expression of surface IgM, activation of NF-kappa-B, and degradation of I-kappa-B-alpha. ***Peptidoglycan*** also induced activation of NF-kappa-B and degradation of I-kappa-B-alpha in macrophage RAW264.7 cells. These ***peptidoglycan*** -induced effects (in contrast to ***endotoxin*** -induced effects) were not inhibited by polymyxin B. Both ***peptidoglycan*** - and ***endotoxin*** -induced activation of NF-kappa-B were inhibited by anti-CD14 mAb. The N-terminal 151 amino acids of CD14 were sufficient for acquisition of full responsiveness to both ***peptidoglycan*** and ***endotoxin*** , but CD14 deletion mutants lacking four small regions within the N-terminal 65 amino acids showed differentially diminished responses to ***peptidoglycan*** and ***endotoxin*** . These results identify CD14 as the functional receptor for ***peptidoglycan*** and demonstrate that similar, but not identical sequences in the N-terminal 65-amino acid region of CD14 are critical for the NF-kappa-B and IgM responses to both ***peptidoglycan*** and ***endotoxin*** .

L19 ANSWER 4 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1995:315650 BIOSIS
DN PREV199598329950
TI Mycoplasma-mediated bone resorption in bone organ cultures.
AU Novak, Josef F. (1); Hayes., James D., Jr.; McMaster, James H.
CS (1) Orthopaedic Res. Lab., Allegheny-Singer Res. Inst., Pittsburgh, PA USA
SO Microbios, (1995) Vol. 81, No. 329, pp. 241-260.
ISSN: 0026-2633.
DT Article
LA English
AB Mycoplasmas have been identified as one of many aetiological factors associated with experimental or human joint disease. Mycoplasma hyorhinis and M. arthritidis but not M. pulmonis were found to cause significant release of calcium from murine long bone explants. The resorption process is inhibited by calcitonin, acetazolamide and by indomethacin. Mycoplasma-derived bone resorbing activity (M-BRA) is not an ***endotoxin*** as its effect is equally potent in cultures of bones obtained from ***endotoxin*** -responsive and - ***unresponsive*** ***mice*** . M-BRA is a high molecular weight compound resistant to proteases and heat but sensitive to hyaluronidase, lipase, detergents and in part to alkali and acid conditions. The active component is associated with the particulate fraction of the mycoplasma and its yield is enhanced by sonication. The damage to the subchondral bone in arthritis associated with a mycoplasma infection may be caused by a potent bone resorption inducing agent of mycoplasma origin.

L19 ANSWER 5 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1995:81342 BIOSIS
DN PREV199598095642
TI Inflammatory mediator stimulation of astrocytes and meningeal fibroblasts induces neuronal degeneration via the nitridergic pathway.
AU Skaper, Stephen D. (1); Facci, Laura; Leon, Alberta
CS (1) Researchlife S.c.p.A., Centro di Ricerca Biomedica, Ospedale Civile, 31033 Castelfranco Veneto Italy
SO Journal of Neurochemistry, (1995) Vol. 64, No. 1, pp. 266-276.
ISSN: 0022-3042.
DT Article
LA English
AB The role of inflammatory cytokines in the pathogenesis of neurological disorders is not entirely clear. The neurotoxic effects of cytokines, and perhaps indirectly ***bacterial*** endotoxins, could be mediated by the stimulation of immunocompetent cells in the brain to produce toxic concentrations of nitric oxide (NO) and reactive nitrogen oxides. NO is a short-lived, diffusible molecule that has a variety of biological activities including vasorelaxation, neurotransmission, and cytotoxicity. Both constitutive and inducible NO synthase has been described in astrocytes in vitro. Here we demonstrate that newborn ***mouse*** cortical astrocytes, when coincubated with neonatal ***mouse*** cerebellar granule cells or hippocampal neurons, induced neurotoxicity upon stimulation with ***endotoxin*** (lipopolysaccharide) (ED-50 30 ng/ml). Astrocytes were ***unresponsive*** to the cytokines tumor necrosis factor-alpha or interleukin-1-beta individually, but exhibited a marked synergistic stimulation in their combined presence. Moreover, meningeal fibroblasts treated with tumor necrosis factor-alpha, but not interleukin-1-beta or lipopolysaccharide, elaborated neurotoxicity for cocultured granule cells (ED-50 30 U/ml). In cocultures of immunostimulated astrocytes or meningeal fibroblasts, neurotoxicity was blocked by the NO synthase inhibitors N-omega-nitro-L-arginine and N-omega-nitro-D-arginine methyl ester, and by oxyhemoglobin, which inactivates NO. Astroglial-induced neurotoxicity was not affected by N-methyl-D-aspartate receptor antagonists. Superoxide dismutase, which degrades superoxide anion, attenuated astrocyte- and fibroblast-mediated neurotoxicity, indicating that endogenous superoxide anion may react with NO to form toxic peroxynitrite and its breakdown products. These findings suggest a potentially important role for glial- and meningeal fibroblast-induced NO synthase in the pathophysiology of CNS disease states of immune or inflammatory origin.

L19 ANSWER 6 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1995:71718 BIOSIS
DN PREV199598086018
TI LPS induces selective translocation of protein kinase C-beta in LPS-responsive ***mouse*** macrophages, but not in LPS-***nonresponsive*** ***mouse*** macrophages.
AU Shinji, Hitomi (1); Akagawa, Kiyoko S.; Yoshida, Takeshi
CS (1) Tokyo Inst. Immunopharmacol. Inc., 3-41-8 Takada, Toshima-ku, Tokyo 171 Japan
SO Journal of Immunology, (1994) Vol. 153, No. 12, pp. 5760-5771.
ISSN: 0022-1767.
DT Article
LA English
AB Translocation of protein kinase C (PKC) after PMA or LPS stimulation has been studied in thioglycolate (TGC)-elicited murine peritoneal macrophages. Among the PKC subtypes we examined (alpha, beta, gamma, delta, and epsilon) by indirect immunostaining and immunoblot analysis, conventional PKC-beta, as well as novel PKC-delta and PKC-epsilon were found to exist in TGC-elicited C3H/HeN ***mouse*** macrophages. Translocation of PKC-beta to the Triton-stable cytoskeleton could be seen in macrophages after stimulation by both PMA and LPS. On the other hand, novel PKCs redistributed only after PMA stimulation. Macrophages obtained from LPS- ***nonresponsive*** C3H/HeJ ***mice*** also exhibited PKC-beta, and the m.w., cellular distribution, and cellular content of this enzyme could not be distinguished from those of C3H/HeN macrophages. These macrophages exhibited PKC-delta and PKC-epsilon, as did the C3H/HeN macrophages. In these macrophages, however, LPS did not induce any remarkable change in the intracellular distribution of PKC-delta and PKC-epsilon or PKC-beta, whereas PMA was able to induce the translocation of PKC-beta to the cytoskeleton. These results suggest that LPS stimulation induces selective redistribution of PKC-beta in LPS-responsive macrophages, whereas a defect related to LPS unresponsiveness exists in C3H/HeJ ***mouse*** macrophages before the PKC activation. Translocation of PKC-beta can be understood to be an important event in LPS signaling in macrophages.

L19 ANSWER 7 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1994:540013 BIOSIS
DN PREV199497553013
TI Modulation of hepatic mRNA levels after administration of lipopolysaccharide and diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP vaccine) to ***mice*** .
AU Ansher, Sherry S. (1); Thompson, Walter
CS (1) HFM-437, Food and Drug Adm., Build. 29, Room 528, 8800 Rockville Pike, Bethesda, MD 20892 USA
SO Hepatology, (1994) Vol. 20, No. 4 PART 1, pp. 984-991.
ISSN: 0270-9139.
DT Article
LA English
AB Administration of whole-cell diphtheria and tetanus toxoids and pertussis vaccine adsorbed (DTP vaccine) caused marked depression in the expression of mRNA for isozymes of cytochrome P-450 in the livers of ***endotoxin*** -responsive and ***nonresponsive*** ***mice*** . The levels of expression of mRNA for a polycyclic aromatic hydrocarbon-inducible (CYP1A2) and an ethanol-inducible (CYP2E1) form of P-450 were reduced by 70% to 80% 8 to 12 hr after vaccination or Bordetella pertussis ***endotoxin*** administration. These effects are preceded by marked increases (threefold to sixfold) in mRNA expression for interleukin-6, interleukin-1 and tumor necrosis factor in both strains of ***mice*** , with maximal increases 1 to 2 hr after injection. This is the first demonstration that levels of cytokine mRNA are altered in the liver in response to DTP vaccine administration. The finding of increased cytokine mRNA in the livers of ***mice*** injected with vaccine supports a role for cytokines as mediators of the decreased levels of cytochrome P-450. In addition, inducible nitric oxide synthase mRNA expression is also increased after vaccine administration, with a peak at 4 hr. The temporal relationship of the increased cytokine mRNA expression, increased nitric oxide synthase and decreased expression of P-450 mRNAs suggests a mechanism by which cytokines mediate the induction of nitric oxide synthase, which increases nitric oxide and decreases the acivities of some cytochromes P-450.

L19 ANSWER 8 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1994:539968 BIOSIS
DN PREV199497552968
TI Tumor necrosis factor involvement in the toxicity of TCDD: The role of ***endotoxin*** in the response.
AU Clark, George C. (1); Taylor, Michael J.
CS (1) Natl. Inst. Environ. Health Sci., P.O. Box 12233, Mail Drop D4-04, Research Triangle Park, NC 27709 USA
SO Experimental and Clinical Immunogenetics, (1994) Vol. 11, No. 2-3, pp. 136-141.
ISSN: 0254-9670.
DT Article
LA English
AB We have previously demonstrated that tumor necrosis factor is involved in the acute toxic effects of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), since therapies designed to attenuate the effects of tumor necrosis factor resulted in reduced mortality and toxicity in ***mice*** exposed to an LD-75 dose of TCDD. The current study addresses whether ***endotoxin*** may be a contributing factor in the cachexia and mortality resulting from TCDD exposure. ***Endotoxin*** - ***nonresponsive*** C3H/HeJ ***mice*** and ***endotoxin*** -responsive C57BL/6 ***mice*** were treated with 350 mu-g/kg TCDD and body weight and mortality were recorded. C3H/HeJ ***mice*** showed no trend in body weight loss ($p = 0.554$), while C57BL/6 ***mice*** demonstrated a statistically significant (p lt 0.01) linear decline in body weight of -0.23 g/ day, resulting in a net loss of 3.5 g over 15 days preceding mortality. Mortality was observed in the C57BL/6 ***mice*** beginning on day 16 with 100% of the ***mice*** dying by the 23rd day while no mortality was observed in C3H/HeJ ***mice*** until the 24th day of the study with only 22% mortality observed. These data further demonstrate that ***endotoxin*** is a contributing factor to the cachexia and lethality of TCDD.

L19 ANSWER 9 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1994:301163 BIOSIS
DN PREV199497314163
TI High in vitro ***endotoxin*** responsiveness of macrophages from an ***endotoxin*** -resistant wild rodent species, Sigmodon hispidus.
AU Dabber, C. Brad (1); Lochmiller, Robert L.; Zhang, Jing-Ren; Qualls, Charles W.; Burnham, Kim
CS (1) Dep. Zool., Oklahoma State Univ., Stillwater, OK 74078 USA
SO Developmental and Comparative Immunology, (1994) Vol. 18, No. 2, pp. 147-153.
ISSN: 0145-305X.
DT Article
LA English
AB It has been reported that macrophages primarily mediate ***endotoxin*** shock and cell death by synthesizing and releasing cytokines, largely tumor necrosis factor (TNF) and interleukin-1 (IL-1). However, macrophages from some laboratory ***mouse*** strains such as C3h/HeN are ***unresponsive*** to ***endotoxin*** both in vivo and in vitro. We found members of a wild rodent species, Sigmodon hispidus, to also be extremely resistant to ***bacterial*** ***endotoxin*** challenge. Intravenous administration of up to 100,000 mu-g/kg body mass of Escherichia coli O26:B6 ***endotoxin*** did not cause lethality in adult S. hispidus. In contrast to the ***endotoxin*** -resistant ***mouse*** strain, peritoneal macrophages derived from S. hispidus were responsive to in vitro ***endotoxin*** challenge as measured by high levels of TNF and IL-1 activity in supernatants of macrophage cultures. Thus, in vitro macrophage responsiveness to ***endotoxin*** does not always indicate high host sensitivity to ***endotoxin*** challenge.

L19 ANSWER 10 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1994:110327 BIOSIS
DN PREV199497123327
TI Sensitive quantitation of ***endotoxin*** by enzyme-linked

immunosorbent assay with monoclonal antibody against Limulus peptide C.
AU Zhang, Gui-Huang; Baek, Leif; Nielsen, Peter E.; Buchardt, Ole; Koch, Claus (1)
CS (1) Statens Seruminstitut, Div. Immunol., 5, Artillerivej, DK-2300 Copenhagen S Denmark
SO Journal of Clinical Microbiology, (1994) Vol. 32, No. 2, pp. 416-422. ISSN: 0095-1137.
DT Article
LA English
AB Limulus peptide C, a 28-amino-acid fragment of coagulogen formed by the reaction of ***endotoxin*** with Limulus amebocyte lysate, was synthesized, and a monoclonal antibody against it was raised. A new microassay for ***endotoxin*** was developed, using this antibody in an enzyme-linked immunosorbent assay for generated peptide C-like immunoreactivity. A linear relationship between absorbance and ***endotoxin*** concentration was obtained. Control standard ***endotoxin*** in water could be detected to a level of 0.001 ***endotoxin*** unit per ml. The ***endotoxin*** levels in plasma samples from normal humans, rabbits, ***mice*** , and guinea pigs were generally found to be below the detection limit of 0.01 ***endotoxin*** unit per ml of plasma. The color and turbidity of specimens did not interfere with the assay. The consumption of Limulus amebocyte lysate in the assay was less than 5% of that in the gel-clot and chromogenic assays. With raw lysate, which was much more stable in solution than chloroform-treated lysate, the assay was still highly sensitive to ***endotoxin*** but was totally ***unresponsive*** to natural glucans. The monoclonal antibody cross-reacted with peptide C-like immunoreactivity generated in Tachypleus amebocyte lysate, which gave equal sensitivity in the ***endotoxin*** assay.

L19 ANSWER 11 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1993:320346 BIOSIS
DN PREV199396028696
TI ***Endotoxin*** -induced expression of ***endotoxin*** binding sites on murine bone marrow cells.
AU Girard, Robert; Pedron, Thierry; Chaby, Richard (1)
CS (1) Equipe "Endotoxines", URA-1116 du CNRS, Batiment 432, Universite de Paris-Sud, 91405 Orsay France
SO Journal of Immunology, (1993) Vol. 150, No. 10, pp. 4504-4513. ISSN: 0022-1767.
DT Article
LA English
AB A variety of binding sites for ***endotoxin*** (LPS) have been identified on leukocytes. However, the sequence of expression of these receptors, and their interrelations, are poorly understood. In this report, we show that in LPS-responsive hosts, interaction of nanomolar concentrations of LPS with bone marrow cells induces the expression of new specific LPS-binding sites. Cells from LPS- ***nonresponsive*** (C3H/HeJ) ***mice*** do not express these receptors after LPS treatment. Experimental differences in the conditions allowing the induction and the detection of these binding sites (influence of Leishmania lipophosphoglycan, role of serum), support the hypothesis that interaction of LPS with primary receptors on bone marrow cells triggers the expression of secondary LPS receptors, and that the two types of receptors have distinct fine specificities.

L19 ANSWER 12 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1993:320303 BIOSIS
DN PREV199396028653
TI Induction of macrophage-mediated production of tumor necrosis factor alpha by an L-form derived from Staphylococcus aureus.
AU Kuwano, Koichi; Akashi, Akira; Matsu-Ura, Ikuko; Nishimoto, Mitsunobu; Arai, Sumio (1)
CS (1) Dep. Microbiol., Kurume Univ. Sch. Med., 67 Asahi-machi, Kurume 830 Japan
SO Infection and Immunity, (1993) Vol. 61, No. 5, pp. 1700-1706. ISSN: 0019-9567.
DT Article
LA English
AB We investigated the capability of an L-form derived form Staphylococcus aureus to induce tumor necrosis factor alpha (TNF-alpha) production in murine peritoneal macrophages. The activity for TNF-alpha induction was found in the membrane fraction of the L-form but not in the cytoplasmal fraction purified by the sucrose step gradient centrifugation. TNF-alpha mRNA was also detected in macrophages stimulated with L-form membranes. L-form induced TNF-alpha production in macrophages from both lipopolysaccharide-responsive and - ***unresponsive*** ***mouse*** strains. Regardless of the presence of polymyxin B, the activity of TNF-alpha induction of L-form was mostly found in the phenol layer, but not in the aqueous layer, both of which were prepared by phenol extraction method. Fractions of L-form membranes representing molecular mass of approximately between 29 and 36 kDa were primarily responsible for inducing the production of TNF-alpha consistently. Moreover, this stimulatory effect was abolished by digestion with Streptomyces griseus protease. In Western blot (immunoblot) analysis with anti-***lipoteichoic*** ***acid*** antibody, two bands (65 and 45 kDa) were observed in the sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the phenol layer, whereas one band (14 kDa) was observed in either the aqueous layer or ***lipoteichoic*** ***acid*** of S. aureus. These results suggest that the component in the membrane of the L-form, distinct from cell wall components such as teichoic acid or lipopolysaccharide, possesses the capability to stimulate TNF-alpha production by macrophages.

L19 ANSWER 13 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1991:501860 BIOSIS
DN BA92:124820
TI LIPOPROTEINS OF BORRELIA-BURGDORFERI AND TREPONEMA-PALLIDUM ACTIVATE
CACHECTIN-TUMOR NECROSIS FACTOR SYNTHESIS ANALYSIS USING A CAT REPORTER
CONSTRUCT.
AU RADOLF J D; NORGARD M V; BRANDT M E; ISAACS R D; THOMPSON P A; BEUTLER B
CS HOWARD HUGHES MED. INST., U. T. SOUTHWESTERN MED. CENT., 5323 HARRY HINES
BLVD., DALLAS, TEXAS 75235-9050.
SO J IMMUNOL, (1991) 147 (6), 1968-1974.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Lipoproteins from two pathogenic spirochetes (Borrelia burgdorferi and Treponema pallidum) induced the biosynthesis of TNF in murine macrophages and in permanently transformed macrophages of the cell line RAW 264.7. Induction was studied by measuring the secretion of biologically active TNF and by measuring the activity of the reporter enzyme chloramphenicol acetyltransferase (CAT) produced within macrophages transfected with an ***endotoxin*** -responsive CAT construct. Several lines of evidence indicated that the induction of TNF and CAT was attributable to the spirochete lipoproteins rather than to contaminating or endogenous LPS: 1) the dose response curves observed for the lipoproteins were markedly different from those obtained with LPS; 2) lipoprotein-mediated activation was unaffected by amounts of polymyxin B that completely neutralized the induction of TNF and CAT by LPS, 3) low concentrations of the lipoproteins induced TNF in macrophages from ***endotoxin*** - ***unresponsive*** C3H/HeJ ***mice*** as effectively as in macrophages from normal C3H/HeN ***mice*** , and 4) isolated spirochete lipoproteins, but not a non-lipoprotein immunogen, were potent inducers of CAT in the transformed macrophages. Moreover, LPS was not detected in the B. burgdorferi lipoprotein mixtures by Limulus amebocyte lysate assay. Proteolytic digestion of the intact ***bacterial*** protein preparations only modestly diminished their ability to activate the cells, suggesting that small lipopeptides comprise the biologically acive portions of the molecules, as is the case with the murein lipoprotein of Escherichia coli. Through their ability to induce TNF production by macrophages, spirochete lipoproteins may play important roles in the development of the local inflammatory changes and the systemic manifestations that characterize syphilis and Lyme disease.

L19 ANSWER 14 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1989:136208 BIOSIS
DN BA87:70861
TI IMMUNOSTIMULATION OF C3H-HEJ LYMPHOID CELLS BY R-CHEMOTYPE LIPOPOLYSACCHARIDE PREPARATIONS.
AU FLEBBE L; VUKAJLOVICH S W; MORRISON D C
CS DEP. MICROBIOL. MOL. GENETICS AND IMMUNOL., UNIV. KANSAS MED. CENT., 39TH
AND RAINBOW BLVD., KANSAS CITY, KANSAS 66103.
SO J IMMUNOL, (1989) 142 (2), 642-652.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Splenocytes from the C3H/HeJ and C57BL/10ScN (nu/nu) inbred ***mouse*** strains have been characterized by a genetic defect in their capacity to proliferate in response to purified protien-free LPS preparations. In this manuscript we provide experimental evidence to support the concept that the refractory state of B cells from ***endotoxin*** - ***unresponsive*** ***mice*** to mitogenic stimulation by LPS does not extend to R-chemotype LPS isolated from a variety of rough strains of Salmonella or Escherichia coli. We present several lines of evidence to suggest that the observed mitogenic activity is not the result of contamination of LPS with lipid A-associated proteins. The mitogenic activity of LPS extracted from rough strain mutant ***bacteria*** (R-LPS) appears to be dependent upon a structural requirement of the LPS in which the 2-keto-3-deoxyoctulosonate linkage of lipid A with core ologosaccharides in intact. Both alkaline and acid hydrolysis or R-LPS abrogates mitogenic activity in C3H/HeJ splenocytes; only the former is effective in reducing activity of the same LPS preparations in histocompatible normal splenocytes. Finally, we have found that the addition of either polymyxin B or S-chemotype LPS to R-LPS-stimulated C3H/Hej splenocytes has only minimal effects on the mitogenic activity of the latter. These combined data would indicate that the concept of LPS-unresponsiveness of the C3H/HeJ and C57B1/10ScN inbred ***mouse*** strains is not necessarily applicable to all protein-free LPS preparations.

L19 ANSWER 15 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1987:400902 BIOSIS
DN BA84:77082

TI INDUCTION BY LIPOPOLYSACCHARIDE OF INTRACELLULAR AND EXTRACELLULAR
INTERLEUKIN 1 PRODUCTION ANALYSIS WITH SYNTHETIC MODELS.
AU LASFARGUES A; LEDUR A; CHARON D; SZABO L; CHABY R
CS INST. BIOCHIM., BAT. 432, UNIV. PARIS-SUD, 91405 ORSAY, FR.
SO J IMMUNOL, (1987) 139 (2), 429-436.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB An attempt was made to identify the molecular structures that are present in ***bacterial*** LPS and induce the production of intracellular and extracellular pools of IL 1 by peritoneal macrophages of the ***mouse*** and by human monocytes. Activities of glycolipids and carbohydrates prepared by synthesis, and structurally related to the hydrophobic (Lipid A) and to the polysaccharide (PS) regions of LPS were compared with those induced by Bordetella pertussis ***endotoxin*** and by fragments derived therefrom. Both isolated regions of this LPS (PS and Lipid A) were able to induce IL 1 synthesis by monocytes and macrophages. Among the synthetic glycolipids employed, propyl-2-deoxy-2-[(3R)-3-hydroxytetradecanamido)-4-O-phosphono-6-O-tetradecanoyl-.beta.-D-glucopyranoside (glycolipid M9) induced IL 1 secretion more efficiently than Lipid A and LPS, whereas the amounts of intracellular IL 1 produced upon induction by these three substances were comparable. Macrophages from C3H/HeJ ***mice*** were ***unresponsive*** to Lipid A and to glycolipid M9, but produced IL 1 when incubated with PS or with a hydrophilic fragment isolated after methanolysis of the ***endotoxin*** . However, all synthetic derivatives of 3-deoxy-D-manno-2-octulosonic acid (KDO) used in this study failed to induce IL 1 production by both ***mouse*** macrophages and human monocytes. The implications of these findings for a more precise comprehension of the molecular mechanism of LPS-induced activation of macrophages, and the relations between the molecular structures required for the induction of IL 1 production vs cytostatic activity in macrophages, are discussed.

L19 ANSWER 16 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1987:316323 BIOSIS
DN BA84:35830
TI LYMPHOCYTE COLLABORATION IS NOT REQUIRED FOR THE INDUCTION OF MURINE
MACROPHAGE PROCOAGULANT BY ***ENDOTOXIN*** .
AU SHANDS J W JR
CS DIV. INFECTIOUS DISEASES, DEP. MED. UNIV. FLORIDA COLL. MED., GAINESVILLE,
FLA. 32610, U.S.A.
SO THROMB RES, (1987) 46 (2), 271-280.
CODEN: THBRAA. ISSN: 0049-3848.
FS BA; OLD
LA English
AB The putative requirement for lymphocytes as instructor cells in the induction of macrophage procoagulant (PCA) by ***endotoxin*** (LPS) was tested on elicited ***mouse*** peritoneal macrophages and on bone marrow-derived macrophages. Percoll purification of thioglycollate macrophages to at least 99.8 percent failed to diminish PCA induction by LPS. Bone marrow macrophages synthesized most PCA in response to LPS when
they constituted more than 95 percent of the cells. In addition, PCA synthesis by these cells was not enhanced by the addition of splenic lymphocytes in a ratio of four to one. Exudate macrophages from ***endotoxin*** ***unresponsive*** C3H/HeJ ***mice*** failed to increase PCA synthesis in the presence of LPS. The addition of responsive C3H/HeN splenic lymphocytes to non-responsive HeJ macrophages did not permit LPS to induce the synthesis of PCA, suggesting the absence of unidirectional lymphocyte-instructed pathway. These data provide no evidence for lymphocyte collaboration in the LPS induction of murine macrophage PCA. LPS appears to induce PCA by acting directly on the macrophage.

L19 ANSWER 17 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1987:65608 BIOSIS
DN BA83:33934
TI INDUCTION OF COLONY-STIMULATING ACTIVITY BY A SYNTHETIC MURAMYL PEPTIDE
SYNERGISM WITH LPS AND ACTIVITY IN C-3H-HEJ ***MICE*** AND IN ***ENDOTOXIN*** -TOLERIZED ***MICE*** .
AU GALELLI A; CHEDID L
CS IMMUNOTHERAPIE EXPERIMENTALE, INSTITUT PASTEUR, 28, RUE DU DR. ROUX, 75724
PARIS CEDEX 15, FRANCE.
SO J IMMUNOL, (1986) 137 (10), 3211-3215.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Injection of MDP into ***mice*** induces a rapid elevation of monocyte-macrophage CSA in the serum. This effect can also be observed in LPS-hyporesponsive C3H/HeJ ***mice*** , MDP and LPS induced CSA synergistically in normal ***mice*** . In contrast to the tolerance that is rapidly observed after repeated administration of LPS, MDP does not lose its capacity of inducing serum CSA after repeated injections. Repeated daily injections of MDP also fail to induce tolerance to the LPS-CSA inducing effect. Furthermore, whereas ***mice*** rendered tolerant to LPS become hyporesponsive to many other ***bacteria*** or ***bacterial*** products, they remain responsive to MDP. These data showing that MDP can act synergistically with another CSA inducer, can be injected repeatedly, and can stimulate ***mice*** ***unresponsive*** to LPS suggest potentially important in vivo applications.

L19 ANSWER 18 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1985:306488 BIOSIS
DN BA79:86484
TI DOWN-REGULATION OF IA EXPRESSION ON MACROPHAGES BY SEA-STAR
ASTERIAS-FORBESI FACTOR.
AU DONNELLY J J; VOGEL S N; PRENDERGAST R A
CS DEPARTMENT OF OPHTHALMOLOGY, UNIVERSITY OF PENNSYLVANIA SCHOOL OF
MEDICINE, SCHEIE EYE INSTITUTE, 51 N. 39TH STREET, PHILADELPHIA, PENN.
19104.
SO CELL IMMUNOL, (1985) 90 (2), 408-415.
CODEN: CLIMB8. ISSN: 0008-8749.
FS BA; OLD
LA English
AB Sea star factor (SSF), a protein of 39,000 Da [dalton] isolated from the coelomocytes of A. forbesi, inhibits the induction of Ia expression on murine macrophages by concanavalin A supernatants. Addition of SSF to cultured macrophages at the same time as the lymphokine preparation significantly reduced the percentage Ia+ cells after 5 days culture, compared to cultures given lymphokine only. Injection i.p. of SSF also reduced the percentage Ia+ peritoneal exudate macrophages by 3/4 in Listeria-infected ***mice*** . Addition of the cyclo-oxygenase inhibitor, indomethacin, to macrophage cultures reversed this Ia-suppressive effect of SSF. Since macrophages from ***endotoxin*** - ***unresponsive*** and ***endotoxin*** -responsive ***mice*** were both sensitive to the Ia-inhibitory effect of SSF, the induction of arachidonic acid metabolism and the inhibition of Ia appear to be independent of the action of ***endotoxin*** . The SSF-induced down regulation of Ia expression may be a major factor in the suppression of primary immune responses to T-dependent antigens previously noted in studies with SSF.

L19 ANSWER 19 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1985:242201 BIOSIS
DN BA79:22197
TI ACQUIRED IMMUNITY TO HEAVY INFECTION WITH MYCOBACTERIUM-BOVIS BCG AND ITS
RELATIONSHIP TO THE DEVELOPMENT OF NONSPECIFIC UNRESPONSIVENESS IN-VITRO.
AU ORME I M; RATCLIFFE M J H; COLLINS F M
CS TRUDEAU INST., P.O. BOX 59, SARANAC LAKE, N.Y. 12983.
SO CELL IMMUNOL, (1984) 88 (2), 285-296.
CODEN: CLIMB8. ISSN: 0008-8749.
FS BA; OLD
LA English
AB ***Mice*** heavily infected with M. bovis BCG rapidly generated an acquired cellular immune response to this infection, as characterized primarily by the emergence of a splenic T-cell population capable of passively transferring substantial levels of adoptive protection against a challenge infection with M. tuberculosis. The emergence of this protective T-cell population was temporally associated with considerable levels of DNA synthesis in vivo in both the spleen and liver, and with the development of an acquired capacity within the animal to express very high levels of nonspecific resistance to secondary intracellular ***bacterial*** infection. Concomitant with the emergence of this acquired response, splenic T cells from infected animals became severely ***unresponsive*** to blastogenic in vitro stimulation with the mitogen phytohemagglutinin and possessed the capacity to suppress the responsiveness of normal T cells in cocultures. Both the unresponsiveness of T cells from infected ***mice*** and their immunosuppressive activity in vitro could be essentially ablated by supplementation of the tissue culture medium with a supernatant containing very high titers of the T-cell growth factor interleukin 2 (IL-2). T cells harvested from these animals at the peak of in vitro unresponsiveness exhibited a substantial capacity to absorb or consume IL[interleukin]-2 from IL-2-containing supernatants. Apparently, ***mice*** heavily infected with BCG acquire an IL-2-dependent T-cell population within the spleen in response to this infection, and the observed in vitro blastogenic unresponsiveness of spleen cells which contain this population may be an artefactual effect arising from the reduction or consumption of available IL-2 within the sustaining culture medium. The relevance of these findings is discussed with particular regard to clinical situations, such as lepromatous leprosy, in which restorative strategies involving the in vivo use of IL-2 are presently being postulated.

L19 ANSWER 20 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1984:194636 BIOSIS
DN BA77:27620
TI THE ABILITY OF LYMPHOKINE AND LIPO POLY SACCHARIDE TO INDUCED PRO
COAGULANT ACTIVITY IN ***MOUSE*** MACROPHAGE CELL LINES.
AU FARRAM E; GECZY C L; MOON D K; HOPPER K

CS KOLLING INST. MED. RES., ROYAL NORTH SHORE HOSP. SYDNEY, ST. LEONARDS,
N.S.W. 2065, AUSTRALIA.
SO J IMMUNOL, (1983) 130 (6), 2750-2756.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB A comparison was made of the abilities of ***mouse*** macrophage cell lines and cultured bone marrow-derived macrophages to respond to lymphokine and lipopolysaccharide (LPS) in the macrophage procoagulant assay (MPCA). ***Mouse*** macrophage cell lines PU5 and WEHI 265 responded to low concentrations of lymphokine and LPS by increased procoagulant activity; the activity of PU5 cells was comparable to that of TG-PEC. Approximately 1/2 of the MPCA induced by lymphokine after 20 h culture was detectable after 2 h with either cell line. J774 was ***unresponsive*** to LPS but responded weakly to lymphokine, and P388D1 and WEHI 274 were ***unresponsive*** to both stimuli as determined by the MPCA test. Addition of purified T cells (5 T cells to 1 macrophage) to the ***unresponsive*** cell lines induced procoagulant activity in the presence of either stimulus, which suggests that cell contact is necessary in some cases. Only J774 cells responded to lymphocyte-derived chemotactic factor (LDCF) or ***endotoxin*** -activated ***mouse*** serum (EAMS) in chemotaxis assays. Immature bone marrow cells responded to chemotactic stimuli, and procoagulant activity was induced with lymphokine after 4 days in culture. Cells cultured for 7 days had about twice as much MPCA, but further culturing did not result in cells with enhanced activity. The procoagulant responsiveness of different macrophage cell lines to lymphokine or LPS may reflect differences in the maturation and differentiation states of these cells.

L19 ANSWER 21 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1984:170173 BIOSIS
DN BA77:3157
TI AN ADHERENT CELL LYSES VIRUS INFECTED TARGETS CHARACTERIZATION ACTIVATION
AND FINE SPECIFICITY OF THE CYTO TOXIC CELL.
AU LETVIN N L; KAUFFMAN R S; FINBERG R
CS DEP. PATHOL., HARVARD MED. SCH., 25 SHATTTUCK ST., BOSTON, MA 02115.
SO J IMMUNOL, (1982) 129 (6), 2396-2401.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB ***Mice*** with defective T lymphocyte function clear a primary reovirus type 1 infection in a normal fashion. Cells that may play a role in the clearance of this primary infection were determined. Macrophages from unprimed ***mice*** lysed reovirus type 1-infected target cells in the absence of specific antibody. Macrophages from nu/nu ***mice*** had higher levels of the lytic activity than macrophages from nu/+ and normal ***mice*** . PEC [peritoneal exudate cell] from ***endotoxin*** - ***nonresponsive*** C3H/HeJ ***mice*** had virtually no antiviral lytic activity; PEC from C3H/FeJ ***mice*** had high levels of such activity. Incubation of PEC from C3H/HeJ ***mice*** overnight in Con A [concanavalin A] supernatants restored this lytic activity. PEC lysed reovirus type 1-infected target cells but not those infected with type 3 reovirus. By using intertypic recombinant viruses, this striking target cell specificity was shown to be a property of the .sigma.1 protein, the viral hemagglutinin.

L19 ANSWER 22 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1982:308455 BIOSIS
DN BA74:80935
TI ENDO TOXIN INDUCED SUPPRESSION OF ERYTHROPOIESIS THE ROLE OF
ERYTHROPOIETIN AND A HEME SYNTHESIS STIMULATING FACTOR.
AU UDUPA K B; LIPSCHITZ D A
CS HEMATOLOGY-ONCOLOGY SECTION, V.A. HOSP., 300 EAST ROOSEVELT ROAD, LITTLE
ROCK, ARK. 72206.
SO BLOOD, (1982) 59 (6), 1267-1271.
CODEN: BLOOAW. ISSN: 0006-4971.
FS BA; OLD
LA English
AB The regulation of erythropoiesis is primarily controlled by erythropoietin (Ep). Recently, other factors that both stimulate and inhibit erythropoiesis were reported. By using an in vitro liquid culture of bone marrow cells, a factor in normal ***mouse*** serum was demonstrated that markedly stimulated heme synthesis by marrow erythroid cells. In this study the role of this heme synthesis stimulating factor (HSF) and Ep in the erythropoietic suppression caused by ***endotoxin*** administration to ***mice*** was examined. Although HSF levels did not alter appreciably after ***endotoxin*** injection, marrow erythroid cells from these animals became ***unresponsive*** to the factor. This was reversed if Ep was added to the culture in vitro or if the hormone was injected into the ***mice*** 18 h prior to harvesting the marrow. This marrow erythroid cell response was identical to that seen in animals in whom Ep levels are markedly reduced, such as that found in exhypoxic polycythemia, and suggested a decrease in the hormone following ***endotoxin*** administration. Additional studies demonstrated that when Ep was injected into ***mice*** 6 h after ***endotoxin*** administration, an increase in femoral erythroid colony-forming units (CFU-E), proerythroblast number and 59Fe incorporation into femoral marrow cells could be demonstrated. The mechanism for suppression of erythropoiesis after ***endotoxin*** injection is apparently a reduction in the level of circulating Ep.

L19 ANSWER 23 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1982:296090 BIOSIS
DN BA74:68570
TI BCG INDUCED ENHANCEMENT OF ENDO TOXIN SENSITIVITY IN C-3H-HEJ ***MICE***
2. T CELL MODULATION OF MACROPHAGE SENSITIVITY TO LIPO POLY SACCHARIDE
IN-VITRO.
AU VOGEL S N; WEEDON L L; WAHL L M; ROSENSTREICH D L
CS DEP. MICROBIOL., UNIFORMED SERVICES, UNIV. HEALTH SCI., 4301 JONES BRIDGE
ROAD, BETHESDA, MD 20014, U.S.A.
SO IMMUNOBIOLOGY, (1982) 160 (5), 479-493.
CODEN: IMMND4. ISSN: 0171-2985.
FS BA; OLD
LA English
AB BCG infection induces a marked increase in lipopolysaccharide (LPS) sensitivity in vivo and will render genetically defective, LPS hyporesponsive, C3H/HeJ ***mice*** almost as sensitive to LPS as normal ***mice*** . The ***endotoxin*** sensitivity of lymphocytes and macrophages from BCG infected ***mice*** were examined. to determine the cellular basis of this effect. The alteration in ***endotoxin*** sensitivity apparently is mediated by a primary effect of BCG infection on T lymphocytes rather than on macrophages. Macrophages from LPS sensitive, BCG-infected C3H/HeJ ***mice*** remain ***unresponsive*** to LPS when tested in vitro. When peritoneal T lymphocytes from these LPS corrected ***mice*** were cocultured with LPS ***unresponsive*** C3H/HeJ macrophages, a conversion to the LPS-responsive state was observed as manifested by the ability of the macrophages to produce interleukin 1 (IL-1) upon LPS stimulation. T cells from normally LPS-responsiver or BCG-infected C3H/HeN ***mice*** , but not from control C3H/H3J ***mice*** , were also able to render C3H/HeJ macrophages sensitive to LPS. This activity was not affected by treatment of the column-purified T cells with anti-macrophage serum plus complement, indicating that the response was not due to residual LPS-responsive macrophages contaminating the T cell preparations. The ability of the T cell suspension to render C3H/HeT macrophages capable of producing IL1 in response to LPS was abrogated by treatment of the T cell preparations with anti-Thy 1.2 plus complement. These findings establish the importance of T lymphocytes in regulating the LPS sensitivity of macrophages in BCG infected C3H/HeT ***mice*** and support the concept that macrophage LPS responsiveness is dependent upon a certain state of macrophage activation which is regulated by lymphocytes.

L19 ANSWER 24 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1982:288786 BIOSIS
DN BA74:61266
TI LIPO POLY SACCHARIDE REGULATION OF THE IMMUNE RESPONSE LIPO POLY
SACCHARIDE INFLUENCE ON ORAL TOLERANCE INDUCTION.
AU MICHALEK S M; KIYONO H; WANNEUEHLER M J; MOSTELLER L M; MCGHEE J R
CS DEP. MICROBIOL., COMPREHENSIVE CANCER CENT., UNIV. ALA. BIRM., UNIVERSITY
STATION, BIRMINGHAM, ALA. 35294.
SO J IMMUNOL, (1982) 128 (5), 1992-1998.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Studies were directed to determine the environmental influence of ***bacterial*** ***endotoxin*** from the indigenous gram-negative flora on gut-associated lympho-reticular tissue (GALT), e.g., Peyer's patches (PP), and the IgA response. Lipopolysaccharide (LPS) responsive and ***nonresponsive*** ***mice*** were compared for induction of systemic unresponsiveness to antigen given for prolonged periods by the oral route (oral tolerance). Daily gastric intubation (GI) of LPS-responsive C3H/HeN ***mice*** with sheep erythrocytes (SRBC) for 2 wk resulted in oral tolerance, similar treatment of LPS-***nonresponsive*** C3H/HeJ ***mice*** primed these animals for anamnestic responses. In vitro studies demonstrated that spleen cells from C3H/HeN ***mice*** given SRBC either by GI or by GI followed by a single i.p. administration of SRBC were ***unresponsive*** to this antigen. Spleen cells from similarly treated C3H/HeJ ***mice*** yielded significant direct (IgM) and indirect (IgG1, IgG2 and IgA) responses to SRBC. Prolonged GI of C3H/HeJ ***mice*** with SRBC did not result in oral tolerance, although lower responses were seen after GI of SRBC for longer periods (28-60 days). Hybrid (F1) ***mice*** from crosses between C3H/H3N and C3H/HeJ animals gave low but significant splenic anti-SRBC plaque-forming cell responses to systemically administered antigen after daily GI with SRBC for a 2 wk period. When SRBC was given by GI for longer periods, F1 ***mice*** gave somewhat lower responses, a pattern similar to that seen with C3H/HeJ ***mice*** . When C3H/HeN ***mice*** were first given SRBC by i.p. administration followed by daily GI for 2 wk, oral tolerance was induced, suggesting that systemic unresponsiveness occurs even in the presence of memory cells. The cellular basis for induction of oral tolerance was suggested by the

finding that splenic T cells from C3H/HeN ***mice*** exhibited significant T suppressor cell activity. T cells from spleen of identically treated C3H/HeJ ***mice*** exhibited mainly T helper cell activity. Oral administration of a thymic-dependent antigen to LPS-responsive ***mice*** apparently induced a T suppressor cell population that suppressed responses to systemically administered antigen. LPS-***nonresponsive*** ***mice*** lack this T suppressor cell pathway and continually respond to oral and systemic administration of antigen.

L19 ANSWER 25 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1980:224821 BIOSIS
DN BA70:17317
TI THE PRIMARY ROLE OF LYMPHO RETICULAR CELLS IN THE MEDIATION OF HOST
RESPONSES TO ***BACTERIAL*** ENDO TOXIN.
AU MICHALEK S M; MOORE R N; MCGHEE J R; ROSENSTREICH D L; MERGENHAGEN S E
CS LAB. MICROBIOL. IMMUNOL., NATL. INST. DENT. RES., BETHESDA, MD. 20205,
USA.
SO J INFECT DIS, (1980) 141 (1), 55-63.
CODEN: JIDIAQ. ISSN: 0022-1899.
FS BA; OLD
LA English
AB ***Mice*** ***unresponsive*** to lipopolysaccharide (LPS) (strain C3H/HeJ) can be rendered LPS-sensitive by the adoptive transfer of bone marrow cells from LPS-sensitive ***mice*** (strain C3H/HeN). This model of adoptive transfer was used to evaluate the contribution of lymphoreticular cells to 5 effects of [Escherichia coli] ***endotoxin*** on the host: immunogenicity, adjuvanticity, lethality, induction of interferon and induction of colony-stimulating factor [CSF]. C3H/HeJ ***mice*** became sensitive to each of these effects after adoptive transfer of bone marrow cells from C3H/HeN ***mice*** . The efficacy of transfer was directly proportional to the dose of X-irradiation and inversely proportional to the number of surviving host stem cells. The most effective dose of radiation was 850 rad, and C3H/HeN .fwdarw. C3H/HeJx chimeras prepared at this dose were as sensitive to LPS for each parameter tested as were the C3H/HeN donors except for a 3-fold greater resistance to lethality than LPS-responsive C3H/HeN ***mice*** . C3H/HeN ***mice*** could also be rendered ***unresponsive*** to LPS by the adoptive transfer of C3H/HeJ bone marrow cells. C3H/HeN chimeras were resistant to all of the effects of LPS studied except for the induction of CSF. Lymphocytes and/or macrophages play a primary role in mediating a number of diverse and seemingly unrelated host responses to ***endotoxin*** .

L19 ANSWER 26 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1980:155494 BIOSIS
DN BA69:30490
TI MACROPHAGE STIMULATION BY ***BACTERIAL*** LIPO POLY SACCHARIDES 3.
SELECTIVE UNRESPONSIVENESS OF C-3H-HEJ MACROPHAGES TO THE LIPID A
DIFFERENTIATION SIGNAL.
AU DOE W F; HENSON P M
CS DEP. MED., UNIV. SYDNEY R. NORTH SHORE HOSP., ST. LEONARDS, N.S.W. 2065,
AUST.
SO J IMMUNOL, (1979) 123 (5), 2304-2310.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Peritoneal macrophages from the ***endotoxin*** - ***unresponsive*** C3H/HeJ substrain of ***mice*** were entirely refractory to activation in vitro by protein-free LPS [Escherichia coli lipopolysaccharide], a defect that was not overcome by co-culture of spleen cells from the responder C3H/St substrain with LPS resistant C3H/HeJ macrophages. The defect in responsiveness appears confined to the lipid A activation signal since C3H/HeJ macrophages were fully activated after in vitro treatment by lipid A protein (LAP)-LPS complex, isolated LAP and BCG. After exposure to allogeneic tumor cells in vivo, C3H/HeJ macrophages were cytotoxic for tumor target cells in vitro. Macrophages from the responder C3H/St strain were fully activated by protein-free LPS to become cytolytic for tumor cells in vitro. C3H/HeJ macrophages, therefore, exhibit a highly selective defect characterized by unresponsiveness to the lipid A activation signal of protein-free LPS and resistance to the toxic effects of high concentrations of LPS that were lethal to the responder C3H/St strain.

L19 ANSWER 27 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1979:201453 BIOSIS
DN BA68:3957
TI MACROPHAGE ACTIVATION FOR TUMOR CYTO TOXICITY TUMORICIDAL ACTIVITY BY
MACROPHAGES FROM C-3H-HEJ ***MICE*** REQUIRES AT LEAST 2 ACTIVATION
STIMULI.
AU RUCO L P; MELTZER M S
CS IMMUNOPATHOL. SECT., LAB. IMMUNOBIOL., NATL. CANCER INST., BETHESDA, MD.
20014, USA.
SO CELL IMMUNOL, (1978) 41 (1), 35-51.
CODEN: CLIMB8. ISSN: 0008-8749.
FS BA; OLD
LA English
AB Macrophages from C3H/HeN ***mice*** treated in vivo with Mycobacterium bovis strain BCG or in vitro with supernatants from antigen-stimulated leukocyte cultures (lymphokines) were cytotoxic to [3-methylcholanthrene induced] tumor cells in vitro. Macrophage tumoricidal activity did not develop after identical in vivo or in vitro treatment of cells from ***endotoxin*** (LPS)- ***unresponsive*** C3H/HeJ ***mice*** . Increasing time of macrophage incubation in lymphokines, concentration of lymphokines or number of lymphokine-treated macrophages added to tumor cells did not evoke tumoricidal activity. Varying time of macrophage collection after BCG infection, numbers of BCG organisms in the infectious inoculum or numbers of macrophages from BCG-infected ***mice*** added to tumor cells also did not evoke cytotoxic activity. The tumoricidal defect of macrophages from C3H/HeJ ***mice*** appeared highly selective: inflammatory responses to BCG infection in C3H/HeN and C3H/HeJ ***mice*** were indistinguishable and no difference was detected between these strains in production of macrophage activation factors. Despite normal inflammatory reactions, normal production of lymphokines and extensive experimental manipulation of single activation stimuli, macrophages from C3H/HeJ ***mice*** did not express tumoricidal activity in vitro. Macrophages from C3H/HeJ ***mice*** could develop tumoricidal activity under appropriate conditions. Macrophages from in vivo immune reactions (BCG infection, Con [concanavalin] A injection), but not from irritant-induced peritoneal exudates, developed full cytotoxic activity after exposure to certain in vitro stimuli. These stimuli included M/ml concentrations of LPS and certain factors in lymphokine supernatants or supernatants from a T[thymus-derived]-cell lymphoma line. The effect of LPS but not that of lymphokines or lymphoma culture supernatants was abrogated by polymyxin B. The ultimate expression of macrophage cytotoxicity may depend on certain signals from the milieu of immune reactions. These expression signals, derived from ***bacterial*** organisms or from soluble mediators of immune responses, provide the necessary and final stimulus for macrophage activation. The tumoricidal defect of macrophages from C3H/HeJ ***mice*** reflects a genetic inability of these cells to respond to environmental expression signals.

L19 ANSWER 28 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1979:155856 BIOSIS
DN BA67:35856
TI RESPONSE OF C-3H-HEJ AND C-3H-HEN ***MICE*** AND THEIR PERITONEAL
MACROPHAGES TO THE TOXICITY OF CHLAMYDIA-PSITTACI ELEMENTARY BODIES.
AU IVINS B E; WYRICK P B
CS DEP. BACTERIOL. IMMUNOL., UNIV. N.C. SCH. MED., CHAPEL HILL, N.C. 27514,
USA.
SO INFECT IMMUN, (1978) 22 (2), 620-622.
CODEN: INFIBR. ISSN: 0019-9567.
FS BA; OLD
LA English
AB Injection i.v. of toxic doses of C. psittaci elementary bodies into ***endotoxin*** -responsive C3H/HeN ***mice*** or ***endotoxin*** - ***nonresponsive*** C3H/HeJ ***mice*** resulted in essentially identical time intervals to death. Inoculation of monolayer cultures of thioglycolate-stimulated peritoneal macrophages from the 2 strains of ***mice*** with 250 elementary bodies/macrophage resulted in immediate host cell toxicity, although the C3H/HeJ macrophages were somewhat less sensitive to elementary body toxicity than were the C3H/HeN macrophages.

L19 ANSWER 29 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1978:190150 BIOSIS
DN BA66:2647
TI ACTIVATION OF ***MOUSE*** LYMPHOCYTES BY ANTI IMMUNO GLOBULIN PART 1
PARAMETERS OF THE PROLIFERATIVE RESPONSE.
AU SIECKMANN D G; ASOFSKY R; MOSIER D E; ZITRON I M; PAUL W E
CS LAB. IMMUNOL., NATL. INST. ALLERGY INFECT. DIS., BETHESDA, MD. 20014, USA.
SO J EXP MED, (1978) 147 (3), 814-829.
CODEN: JEMEAV. ISSN: 0022-1007.
FS BA; OLD
LA English
AB Spleen cell cultures from young adult ***mice*** of a variety of strains were stimulated to incorporate tritiated thymidine ([3H]TdR) by a goat anti- ***mouse*** IgM antiserum and by purified anti-.mu. antibodies prepared from this serum. This stimulation depended on the anti-.mu. activity of the antiserum. Ultracentrifuged anti-.mu. and F(ab')2 fragments of anti-.mu. were stimulatory. The anti-.mu. preparation lacked detectable ***endotoxin*** contamination and stimulated response by 2 strains (C57BL/10ScCr and C3H/HeJ) which are ***unresponsive*** to the mitogenic effects of ***endotoxin*** . It failed to stimulate a response by cells from a ***mouse*** strain (CBA/N) which responds to ***endotoxin*** . In addition purified goat anti- ***mouse*** .gamma.,.kappa. antibodies and rabbit anti-***mouse*** .kappa.-antibodies stimulated uptake of [3H]TdR by ***mouse*** spleen cells, although to a lesser degree than the anti-.mu. preparation. The cell density, culture requirements and kinetics of the

response are presented.

L19 ANSWER 30 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1978:160422 BIOSIS
DN BA65:47422
TI DEFECTIVE TUMORICIDAL CAPACITY OF MACROPHAGES FROM C-3H-HEJ ***MICE***

AU RUCO L P; MELTZER M S
CS IMMUNOPATHOL. SECT., LAB. IMMUNOBIOL., DIV. CANCER BIOL. DIAGN., NATL.
CANCER INST., BETHESDA, MD. 20014, USA.
SO J IMMUNOL, (1978) 120 (1), 329-334.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA English
AB Peritoneal macrophages from C3H/HeN ***mice*** treated i.p. with T [thymus derived] cell mitogens or viable BCG organisms were cytotoxic to syngeneic tumor cells in vitro. Macrophages from ***endotoxin*** -***unresponsive*** C3H/HeJ ***mice*** treated with BCG or T cell mitogens were not tumoricidal. Unlike cells from C3H/HeN ***mice*** , macrophages from C3H/HeJ ***mice*** could not be activated for tumor cytotoxicity after in vitro treatment with ***bacterial*** [Escherichia coli] endotoxins or with lymphokine-rich supernatants. The subnormal induction of cytotoxic macrophages after in vitro or in vivo treatments in C3H/HeJ ***mice*** appears to be a highly selective defect. Macrophage responses (yield, phagocytosis or peroxidase staining) in inflammatory exudates induced by BCG, T cell mitogens or heterologous serum in C3H/HeJ or C3H/HeN ***mice*** were identical. C3H/HeJ macrophages also responded normally in vitro to chemotactic lymphokines. Thus, C3H/HeJ macrophages possess a profound and selective defect in tumoricidal capacity. This defect was not dependent upon exogenous endotoxins. Defective macrophage cytotoxic responses may reflect non-LPS [lipopolysaccharide] related functions regulated by the LPS gene.

L19 ANSWER 31 OF 39 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1977:149752 BIOSIS
DN BA63:44616
TI GENETIC CONTROL OF BONE MARROW DERIVED CELL ACTIVATION BY ***BACTERIAL*** LIPO POLY SACCHARIDE IS MEDIATED BY MULTIPLE DISTINCT
GENES OR ALLELES.
AU GLODE L M; ROSENSTREICH D L
SO J IMMUNOL, (***1976 (RECD 1977)***) 117 (6), 2061-2066.
CODEN: JOIMA3. ISSN: 0022-1767.
FS BA; OLD
LA Unavailable
AB Closely related C3H ***mouse*** strains (11) were examined for differences in their DNA synthetic response to a highly discriminatory ***endotoxin*** , LPS Escherichia coli K-235. Strains of the C3H line were high, intermediate or low responders to ***endotoxin*** . Strains C3H/St, C3H/Bi and C3H/CR were high responders. Strains C3H/He, C3HfB/He,
C3H/Hen, C3Heb/Fej, C3H/DiSn and C3H/Avy were intermediate responders, suggesting that a mutation producing decreased LPS responsiveness occurred in the C3H/He(C3H/An) strain between 1931 and 1945. Strains C3H/HeJ and C3H/Bts were ***unresponsive*** due to a mutation that occurred between 1960 and 1968. Breeding experiments among high, intermediate and low responding strains documented probable codominant genetic control by the genes or alleles in the C3H/HeN and C3H/HeJ strains. In the C3H/HeN .times. C3H/St cross, dominance of the C3H/St gene over the C3H/He gene was documented; the C3H/HeJ .times. C3H/St cross indicated codominance of these 2 genes. These findings may represent 3 alleles or 3 distinct genes in C3H ***mice*** . A 2nd X-linked gene locus was documented in the CBA/N strain which also causes impaired B [bone marrow-derived] cell responsiveness to LPS E. coli K235 in serum-free conditions. The abnormal gene products in the CBA/N and C3H/HeJ strains exhibit complementarity since F1 female animals from the cross between these 2 ***unresponsive*** strains are responsive to LPS. There is apparently at least 1 distinct X-linked gene locus and 3 additional autosomal genes or 3 possible alleles at one or more autosomal loci which determine the LPS sensitivity of murine B cells.

L19 ANSWER 32 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 93320730 EMBASE
DN 1993320730
TI Surface expression of human CD14 in Chinese hamster ovary fibroblasts imparts macrophage-like responsiveness to ***bacterial*** ***endotoxin*** .
AU Golenbock D.T.; Liu Y.; Millham F.H.; Freeman M.W.; Zoeller R.A.
CS Maxwell Finland Infectious Dis. Lab., 774 Albany St.,Boston, MA 02118, United States
SO Journal of Biological Chemistry, (1993) 268/29 (22055-22059).
ISSN: 0021-9258 CODEN: JBCHA3
CY United States
DT Journal; Article
FS 029 Clinical Biochemistry
LA English
SL English
AB Cardiovascular collapse associated with Gram-negative septicemia is believed to result from the stimulation of phagocytes by ***bacterial*** lipopolysaccharide (***endotoxin*** , LPS). It remains unclear how ***endotoxin*** activates phagocytes, but recent evidence suggests the involvement of the glycosyl phosphatidylinositol-linked myelocyte antigen, CD14. We report that transfection of human CD14 into Chinese hamster ovary fibroblasts transfers macrophage-like responsiveness to otherwise LPS-***unresponsive*** cells. These data demonstrate that LPS-induced responsiveness can be transferred to a heterologous non-responder cell type by expression of a single leukocyte- specific gene product.

L19 ANSWER 33 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 92219648 EMBASE
DN 1992219648
TI Cholera toxin as a mucosal adjuvant: Effects of H-2 major histocompatibility complex and Ips genes.
AU Elson C.O.
CS Division of Gastroenterology, University of Alabama,Birmingham, AL 35294, United States
SO Infection and Immunity, (1992) 60/7 (2874-2879).
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB In previous studies we found that cholera toxin (CT) can act as a mucosal adjuvant; i.e., it can stimulate an intestinal secretory immunoglobulin A (S- IgA) response to an unrelated protein antigen when both are fed together to ***mice*** . The purpose of this study was to determine whether the mucosal adjuvanticity of CT is restricted by either H-2 major histocompatibility complex or Ips genes by using congenic inbred strains that differ at only a single genetic locus. Groups of five ***mice*** each were fed saline, CT (10 .mu.g), keyhole limpet hemocyanin (KLH) (5 mg), or both CT and KLH on four different days, and samples of intestinal secretions and plasma were obtained 1 week after the last feeding. In the ***mice*** fed both CT and KLH, the intestinal S-IgA anti-KLH response was higher in H-2b congenic strains than in H-2(k) congenic strains, and in addition there was a highly significant positive correlation between the intestinal S-IgA anti-KLH and S-IgA anti-CT responses in the intestinal secretions of individual ***mice*** . Similarly, in the Ips congenic strains, ***mice*** of the ***endotoxin*** -responsive strain that were fed both CT and KLH had substantially higher S-IgA and plasma IgG responses to KLH than did ***mice*** of the ***endotoxin*** - ***unresponsive*** strain. The effect of CT on the induction of oral tolerance to KLH in the H-2 congenic strains was also examined. In contrast to the results above, the abrogation of oral tolerance to KLH by CT occurred in all strains regardless of H-2 haplotype. Similarly, the adjuvant effect of CT on plasma IgG anti-KLH responses after both were given together intraperitoneally was not restricted by H-2. I conclude that the mucosal adjuvanticity of CT is influenced by both the H-2 and Ips genetic loci and that it appears to depend on a vigorous mucosal immune response to CT itself.

L19 ANSWER 34 OF 39 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 76045860 EMBASE
DN 1976045860
TI ***Endotoxin*** stimulated immune response to modified lymphoma cells.
AU Prager M.D.; Ludden C.M.; Mandy W.J.; et al.
CS Dept. Surg., Univ. Texas Southwest. Med. Sch., Dallas, Tex. 75235, United States
SO Journal of the National Cancer Institute, (1975) 54/3 (773-775).
CODEN: JNCIAM
DT Journal
FS 037 Drug Literature Index
016 Cancer
005 General Pathology and Pathological Anatomy
026 Immunology, Serology and Transplantation
025 Hematology
LA English
AB ***Bacterial*** ***endotoxin*** was administered with iodoacetamide modified P1798 lymphoma cells to immunize syngenic BALB/cJ ***mice*** against this lymphoma to which they are naturally ***unresponsive*** . 3 Or 4 vaccinations with ***endotoxin*** (6.6 .mu.g/injection) alone or the modified cells alone did not produce host resistance. A significant number (30%) of ***mice*** receiving both ***endotoxin*** and modified cells rejected a subsequent implant of viable tumor cells. Even those ***mice*** having progressive tumor growth exhibited prolonged survival. High doses of ***endotoxin*** given with the modified P1798 cells caused 70-75% of the ***mice*** to reject the tumor implants. When resistance developed, antibodies reacting with tumor cell membrane were demonstrable. These results indicate that B-lymphocyte stimulators can produce an effective immune response against lymphoma cells.

L19 ANSWER 35 OF 39 CAPLUS COPYRIGHT 2003 ACS
AN 1992:4953 CAPLUS
DN 116:4953
TI Gamma interferon production in ***endotoxin*** -responder and -nonresponder ***mice*** during infection
AU Freudenberg, Marina A.; Kumazawa, Yoshio; Meding, Sally; Langhorne, Jean; Galanos, Chris
CS Max-Planck-Inst. Immunbiol., Freiburg, D-7800, Germany
SO Infection and Immunity (***1991***), 59(10), 3484-91

CODEN: INFIBR; ISSN: 0019-9567
DT Journal
LA English
AB The prodn. of .gamma. interferon (IFN-.gamma.) in response to infection and to a no. of other agents was compared in Lpsn (C3H/HeN and C57BL/10ScSn) and Lpsd (C3H/HeJ and C57BL/10ScCr) ***mouse*** strains.
Large differences in IFN-.gamma. prodn. were obsd. between C57BL/10ScCr ***mice*** and the other ***mouse*** strains. With the exception of C57BL/10ScCr, all ***mouse*** strains, including C3H/HeJ, exhibited transient levels of IFN-.gamma. during infection with Salmonella typhimurium. Spleen cells of these ***mice*** , explanted on day 3 of infection, produced in vitro IFN-.gamma. spontaneously; this prodn. was enhanced considerably by heat-killed S. typhimurium, heat-killed Propionibacterium acnes, Con A, or lipopolysaccharide (LPS). These stimuli, except for LPS, also induced IFN-.gamma. prodn. in cultures of normal spleen cells from noninfected animals. In contrast, C57BL/10ScCr ***mice*** produced no IFN-.gamma. following infection with S. typhimurium. Also, spleen cells of these ***mice*** , explanted on day 3 of infection, exhibited no spontaneous IFN-.gamma. prodn. A marginal response was obtained by addnl. stimulation of the cells with killed S. typhimurium, and a moderate response was obtained with Con A. Normal spleen cells from noninfected C57BL/10ScCr ***mice*** showed no IFN-.gamma. response to killed S. typhimurium, killed P. acnes, or LPS and only a low response to Con A. Impaired IFN-.gamma. prodn. in C57BL/10ScCr ***mice*** was also evident during infection with Plasmodium chabaudi chabaudi, with which a low IFN-.gamma. response was seen only occasionally. Also, spleen cells from infected animals (days 2-8 after infection) exhibited only a very low level of IFN-.gamma. prodn. in vitro; however, this prodn. could be enhanced further by Con A. In comparison, C57BL/10ScSn ***mice*** infected with P. chabaudi chabaudi produced significant amts. of IFN-.gamma.. Spleen cells explanted from infected animals produced IFN-.gamma. spontaneously in vitro; this prodn. was enhanced further by killed P. acnes and Con A. Thus, in addn. to the defect in LPS responsiveness, C57BL/10ScCr ***mice*** possess a defect in IFN-.gamma. prodn. in response to different stimuli. During infection, IFN-.gamma. prodn. and sensitization to LPS occurred in parallel. Infected Lpsn ***mice*** exhibited enhanced sensitivity and infected Lpsd C3H/HeJ ***mice*** exhibited reasonable sensitivity to the lethal effects of LPS. Lpsd C57BL/10ScCr ***mice*** remained resistant to LPS when infected with S. typhimurium and exhibited only marginal sensitivity when infected with P. chabaudi chabaudi.

L19 ANSWER 36 OF 39 CAPLUS COPYRIGHT 2003 ACS
AN 1990:491081 CAPLUS
DN 113:91081
TI Lipoamino acids which are similar to ***bacterial*** ***endotoxin*** in both structure and biological activity related to physiological function
AU Kawai, Y.; Akagawa, K.; Yano, I.
CS Dep. Bacteriol., Natl. Inst. Health, Tokyo, Japan
SO Advances in Experimental Medicine and Biology (***1990***), 256(Endotoxin), 159-62
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal
LA English
AB Two lipoamino acids from Flavobacterium augmented the mitogenicity of B-lymphocytes from both lipopolysaccharide (LPS)-responsive and ***nonresponsive*** ***mice*** and activated ***mouse*** peritoneal macrophages to produce tumor necrosis factor, PGE2, and interleukin 1, all mediators of endotoxemia. As with LPS, the sensitivity of macrophages to the lipoamino acids was augmented by the treatment of cells with interferon-.gamma.. The partial difference between the activities of LPS and lipoamino acids may be due to their structural differences. Lipamino acids could be useful immunoactivators.

L19 ANSWER 37 OF 39 CAPLUS COPYRIGHT 2003 ACS
AN 1983:420829 CAPLUS
DN 99:20829
TI Interaction of latex-insolubilized endotoxins with murine macrophages: phagocytic responses of ***endotoxin*** -responsive (C3HeB/FeJ) and -***unresponsive*** (C3H/HeJ) macrophages in vitro
AU Lubinsky-Mink, Sharon; Munkenbeck, Priscilla; Morrison, David C.
CS Sch. Med., Emory Univ., Atlanta, GA, USA
SO Journal of the Reticuloendothelial Society (1974-1981) (***1983***), 33(5), 353-67
CODEN: JRSODF; ISSN: 0033-6890
DT Journal
LA English
AB Insolubilized lipopolysaccharides (LPS) were prepd. by covalently coupling LPS from polysaccharide-deficient Salmonella minnesota R595 and polysaccharide-rich Escherichia coli 055:B5 to carboxylated latex particles. The stability of these LPS-latex complexes was detd. using several assays to detect sol. LPS following incubation at ambient and elevated temps. Resident and thioglycollate-elicited macrophages from both LPS-responder C3HeB/FeJ and LPS nonresponder C3H/HeJ ***mice*** were examd. for their capacity to phagocytose the LPS particles following in vitro culture for various time periods. Uptake was demonstrated by an increase in the no. of particles within the macrophages with increasing time of incubation. Rough polysaccharide-deficient LPS-latex particles were more readily phagocytosed than control particles, whereas smooth polysaccharide-rich LPS particles were phagocytosed less readily than the controls. Qual. similar results were found in the relative rate of uptake of particles by the macrophages from the ***endotoxin*** -responsive and - ***unresponsive*** ***mouse*** strains.

L19 ANSWER 38 OF 39 CAPLUS COPYRIGHT 2003 ACS
AN 1981:77897 CAPLUS
DN 94:77897
TI LPS regulation of the immune response: cellular and molecular basis of adjuvanticity and the role of suppressor T cells on host responses
AU McGhee, J. R.; Michalek, S. M.; Kiyono, H.; Farrar, J. J.; Rosenstreich, D. L.; Mergenhagen, S. E.
CS Inst. Dent. Res., UAB, Birmingham, AL, 35294, USA
SO Nat. Toxins, Proc. Int. Symp. Anim., Plant Microb. Toxins, 6th (***1980***), Meeting Date 1979, 279-86. Editor(s): Eaker, D.; Waldstroem, T. Publisher: Pergamon, Oxford, Engl.
CODEN: 44VRAY
DT Conference
LA English
AB The contribution of macrophages (M.phi.) and T cells and certain of their mediators to adjuvanticity by utilizing lipopolysaccharide (LPS) responsive (C3H/HeN and C57BL/10 Sn) and ***nonresponsive*** (C3H/HeJ and C57BL/10 ScN) ***mice*** was evaluated. Purified T and B spleen cells were obtained by glass and nylon wool column chromatog., while M.phi. were obtained from irradiated (1000 R) spleen cells. Appropriate mixts. of either LPS responsive or ***nonresponsive*** cells were cultured with either haptenated or normal heterologous erythrocytes and LPS. Adjuvanticity was obtained only when LPS responsive M.phi. and T cells (from either C3H/HeN or C57BL/10 Sn spleen) were cultured with B cells from either responder or nonresponder animals. Lymphocyte activating factor (LAF) (Interleukin 1, IL 1) plus LPS gave higher anti-SRC plaque-forming cell (PFC) responses only in the presence of T cells from LPS responsive ***mice*** . Further, antigen-induced and LPS-augmented PFC helper factor gave anti-SRC PFC responses in ***nonresponsive*** nude (C57BL/10 ScN) spleen cell cultures, suggesting that LPS-induced adjuvanticity may be mediated by increasing the prodn. of LAF (IL 1) and PFC helper factor. The role of suppressor T cells on immunogenic and mitogenic responses to LPS was also investigated. Thus, significant suppression of lipid A effects is manifested by gut-assocd. lymphoid tissue T cells, indicating that the normal Gram-neg. gut flora induces a cell population which can regulate B cell responses to ***bacterial*** ***endotoxin*** .

L19 ANSWER 39 OF 39 CAPLUS COPYRIGHT 2003 ACS
AN 1968:76545 CAPLUS
DN 68:76545
TI Modification of an ***endotoxin*** effect by esters
AU Margherita, S.; Patnode, Robert A.
CS Univ. of Oklahoma Med. Sch., Oklahoma City, OK, USA
SO Experientia (***1968***), 24(3), 267-8
CODEN: EXPEAM; ISSN: 0014-4754
DT Journal
LA English
AB Ethyl stearate (60 mg.) emulsified with Tween 80 (0.8% vol./vol.) and glucose (5% wt./vol.) was injected into the peritoneal cavities of ***mice*** paralyzed immunologically by the i.p. injection of pneumococcal polysaccharide type 8 (500 .mu.g.), and 14 days after the injection of the polysaccharide only 1 of 11 ***mice*** had serum antibody when assayed by indirect red cell hemolysis, with complement as lytic factor. In another group of paralyzed ***mice*** receiving ***endotoxin*** from gram-neg. ***bacteria*** (50 .mu.g. i.p.) 20 hrs. before challenge with an immunizing dose of antigen (0.5 .mu.g.i.p.), 67% of these ***mice*** showed the appearance of antibody. When a 3rd group of paralyzed ***mice*** was given ethyl stearate (60 mg.i.p.) 25 hrs. prior to the ***endotoxin*** , only 30% of these animals had antibody after challenge; further, when the total dose of the ester was increased to 200 mg. none of the ***mice*** produced antibody. Unlike ***endotoxin*** , zirconium (7.8 mg.i.p.) did not cause a termination of immunologic unresponsiveness. The reticuloendothelial system seems to be involved in the ***endotoxin*** -induced termination of immunologic unresponsiveness. Ethyl stearate decreases the capacity of ***unresponsive*** animals to respond to ***endotoxin*** .

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NEWS 23 Sep 03 JAPIO has been reloaded and enhanced
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NEWS 35 Dec 04 CSA files on STN
NEWS 36 Dec 17 PCTFULL now covers WPIPCT Applications from 1978 to date
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MACROPHAGE ACTIVATING LIPOPEPTIDE)

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L3 ANSWER 1 OF 106 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 1998193776 EMBASE
TI Treponema pallidum and Borrelia burgdorferi lipoproteins and synthetic lipopeptides activate monocytic cells via a CD14-dependent pathway distinct from that used by lipopolysaccharide.
AU Sellati T.J.; Bouis D.A.; Kitchens R.L.; Darveau R.P.; Pugin J.; Ulevitch R.J.; Gangloff S.C.; Goyert S.M.; Norgard M.V.; Radolf J.D.
CS Dr. J.D. Radolf, Division of Infectious Diseases, University of Texas, Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9113, United States. jradol@mednet.swmed.edu
SO Journal of Immunology, (1 Jun 1998) 160/11 (5455-5464).
Refs: 77
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB Lipoproteins of Treponema pallidum and Borrelia burgdorferi possess potent proinflammatory properties and, thus, have been implicated as major proinflammatory agonists in syphilis and Lyme disease. Here we used purified B. burgdorferi outer surface protein A (OspA) and synthetic lipopeptides corresponding to the N-termini of OspA and the 47-kDa major ***lipoprotein*** immunogen of T. pallidum to clarify the contribution of CD14 to monocytic cell activation by spirochetal lipoproteins and lipopeptides. As with LPS, ***mouse*** anti-human CD14 Abs blocked the activation of 1,25-dihydroxyvitamin D3-matured human myelomonocytic THP-1 cells by OspA and the two lipopeptides. The existence of a CD14-dependent pathway was corroborated by using undifferentiated THP-1 cells transfected with CD14 and peritoneal macrophages from CD14-deficient BALB/c ***mice*** . Unlike LPS, cell activation by lipoproteins and lipopeptides was serum independent and was not augmented by exogenous LPS-binding protein. Two observations constituted evidence that LPS and ***lipoprotein*** /lipopeptide signaling proceed via distinct transducing elements downstream of CD14: 1) CHO cells transfected with CD14 were exquisitely sensitive to LPS but were ***lipoprotein*** /lipopeptide ***nonresponsive*** ; and 2) substoichiometric amounts of deacylated LPS that block LPS signaling at a site distal to CD14 failed to antagonize activation by lipoproteius and lipopeptides. The combined results demonstrate that spirochetal lipoproteins and lipopeptides use a CD14-dependent pathway that differs in at least two fundamental respects from the well-characterized LPS recognition pathway.

L3 ANSWER 2 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 1998:512317 BIOSIS
DN PREV199800512317
TI ***Lipoprotein*** release by bacteria: Potential factor in bacterial pathogenesis.
AU Zhang, Hongwei; Niesel, David W.; Peterson, Johnny W.; Klimpel, Gary R. (1)
CS (1) Dep. Microbiol. Immunol, Univ. Texas Med. Branch, Galveston, TX 77555-1070 USA
SO Infection and Immunity, (***Nov., 1998***) Vol. 66, No. 11, pp. 5196-5201.
ISSN: 0019-9567.
DT Article
LA English
AB ***Lipoprotein*** (LP) is a major component of the outer membrane of bacteria in the family Enterobacteriaceae. LP induces proinflammatory cytokine production in macrophages and lethal shock in LPS-responsive and - ***nonresponsive*** ***mice*** . In this study, the release of LP from growing bacteria was investigated by immuno-dot blot analysis. An immuno-dot blot assay that could detect LP at levels as low as 100 ng/ml was developed. By using this assay, significant levels of LP were detected in culture supernatants of growing Escherichia coli cells. During mid-logarithmic growth, approximately 1 to 1.5 mug of LP per ml was

detected in culture supernatants from E. coli. In contrast, these culture supernatants contained 5-to 6 mug/ml of lipopolysaccharide (LPS). LP release was not unique to E. coli. Salmonella typhimurium, Yersinia enterocolitica, and two pathogenic E. coli strains also released LP during in vitro growth. Treatment of bacteria with the antibiotic ceftazidime significantly enhanced LP release. Culture supernatants from 5-h cultures of E. coli were shown to induce in vitro production of interleukin-6 (IL6) by macrophages obtained from LPS- ***nonresponsive*** C3H/HeJ ***mice*** . In contrast, culture supernatants from an E. coli LP-deletion mutant were significantly less efficient at inducing IL-6 production in C3H/HeJ macrophages. These results suggest, for the first time, that LP is released from growing bacteria and that this released LP may play an important role in the induction of cytokine production and pathologic changes associated with gram-negative bacterial infections.

L3 ANSWER 3 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 1998:496966 BIOSIS
DN PREV199800496966
TI Induction of nitric oxide production and tumoricidal properties in murine macrophages by a new synthetic lipopeptide JBT3002 encapsulated in liposomes.
AU Eue, Ines; Kumar, Rakesh; Dong, Zhongyun; Killion, Jerald J.; Fidler, Isaiah J. (1)
CS (1) Dep. Cell Biol., Box 173, Univ. Texas M. D. Anderson Cancer Cent., 1515 Holcombe Blvd., Houston, TX 77030 USA
SO Journal of Immunotherapy, (***Sept., 1998***) Vol. 21, No. 5, pp. 340-351.
DT Article
LA English
AB We studied activation to the tumoricidal state of murine peritoneal macrophages by liposomes containing a new synthetic analogue, JBT3002, of a ***lipoprotein*** from the outer wall of a gram-negative bacterium. The liposomes containing JBT3002 or CGP31362 were superior to liposomes containing muramyl tripeptide phosphatidylethanolamine (MTP-PE) for tumoricidal activation in three ways. First, efficient macrophage activation required lower concentrations of JBT3002 or CGP31362 than MTP-PE. Second, macrophage activation by JBT3002 was less dependent on priming by interferon-gamma. Third, MLV-JBT3002 activated tumoricidal properties in both lipopolysaccharide (LPS)-responsive and LPS- ***nonresponsive*** macrophages. The activation of tumoricidal properties by MLV-JBT3002 depended on protein tyrosine kinase (PTK) activity associated with phosphorylation of tyrosine. The major mechanism for tumoricidal activity in macrophages incubated with MLV-JBT3002 was due to increased activity of inducible nitric oxide synthase (iNOS) and, hence, production of nitric oxide (NO). We base this conclusion on the results of several experiments. First, MLV-JBT3002 was not directly toxic to tumor target cells. Second, the specific iNOS inhibitor NG-monomethyl-L-arginine abrogated tumor cell lysis by MLV-JBT3002-treated macrophages. Third, macrophages from iNOS knockout ***mice*** did not lyse tumor cells, even after incubation with high concentrations of MLV-JBT3002. These data suggest that liposomes containing the synthetic bacterial lipopeptide JBT3002 are potent activators of macrophage tumoricidal properties.

L3 ANSWER 4 OF 106 CAPLUS COPYRIGHT 2003 ACS
AN 1997:736541 CAPLUS
DN 128:33632
TI Bacterial ***lipoprotein*** and lipopolysaccharide act synergistically to induce lethal shock and proinflammatory cytokine production
AU Zhang, Hongwei; Peterson, Johnny W.; Niesel, David W.; Klimpel, Gary R.
CS Dep. of Microbiology and Immunology, University of Texas Medical Branch, Galveston, TX, 77555, USA
SO Journal of Immunology (***1997***), 159(10), 4868-4878
CODEN: JOIMA3; ISSN: 0022-1767
PB American Association of Immunologists
DT Journal
LA English
AB Septic shock is a major cause of death in the world. Although much is known about the role of LPS in septic shock, little is known about the role of other bacterial components. ***Lipoprotein*** (LP) is a major component of bacteria in the family Enterobacteriaceae. LP purified from Escherichia coli was shown to induce TNF-.alpha. and IL-6 prodn. in peritoneal exudate macrophages obtained from LPS-responsive (C3H/HeOuJ) and LPS- ***nonresponsive*** (C3H/HeJ) ***mice*** . LP AND LPS acted synergistically to induce cytokine prodn. not only in C3H/HeOuJ macrophages but also in C3H/HeJ macrophages. These results suggest that LPS can induce cellular signaling in C3H/HeJ macrophages, and that LPS and LP activate macrophages via different receptors and/or signaling pathways. The role LP plays in septic shock was investigated using the ***mouse*** D-galactosamine model. LP induced lethal shock and in vivo prodn. of TNF-.alpha. and IL-6 in both LPS-responsive and LPS- ***nonresponsive*** ***mice*** . LPS failed to induce lethal shock or in vivo cytokine prodn. in C3H/HeJ ***mice*** . However, LP and LPS acted synergistically in inducing lethal shock and in vivo cytokine prodn. in both LPS-responsive and LPS- ***nonresponsive*** ***mice*** . Finally, a heat-killed prepn. of an E. coli mutant strain that lacked LP was shown to be less efficient than heat-killed wild-type E. coli at inducing lethal shock in C3H/HeJ ***mice*** . Collectively, these results suggest that LP and LPS induce cytokine prodn. via different mechanisms and that LP plays an important role in septic shock induced by bacteria in the family Enterobacteriaceae.

L3 ANSWER 5 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
3
AN 1997:393521 BIOSIS
DN PREV199799692724
TI The ***endotoxin*** of Helicobacter pylori is a modulator of host-dependent gastritis.
AU Sakagami, Takashi; Vella, Jennifer; Dixon, Michael F.; O'Rourke, Jani; Radcliff, Fiona; Sutton, Philip; Shimoyama, Takashi; Beagley, Ken; Lee, Adrian (1)
CS (1) Sch. Microbiol. Immunol., Univ. New South Wales, Sydney 2052 Australia
SO Infection and Immunity, (1997) Vol. 65, No. 8, pp. 3310-3316.
ISSN: 0019-9567.
DT Article
LA English
AB Atrophic gastritis caused by Helicobacter pylori is the precursor lesion in the development of intestinal-type gastric adenocarcinoma. In animal models, atrophic gastritis induced by Helicobacter felis has been shown to be host dependent, developing in some ***mouse*** strains and not in others. The lipopolysaccharide (LPS) of H. pylori has been suggested to play a role in the induction of gastritis. The goal of this study was to compare the inflammation induced by long-term infection of the C3H/He and the C3H/HeJ strains of ***mice*** with H. felis. C3H/HeJ ***mice*** are ***unresponsive*** to LPS. Six months after infection, severe atrophic gastritis had developed in the body mucosae of all infected C3H/He ***mice*** , with replacement of parietal and chief cells. Atrophy was associated with a loss of the H. felis from the antral mucosa. In contrast, no atrophy was seen in the infected C3H/HeJ non-LPS responder animals, and heavy colonization of the antrum remained. There were no significant differences between both the quantitative and qualitative serum immunoglobulin G (IgG) and salivary IgA levels in both strains of ***mice*** . The main difference between the two strains of long-term-infected ***mice*** was a lack of macrophage infiltration in the lamina propria. Immunization induced good protective immunity to challenge with viable H. felis. Helicobacter-induced, host-dependent gastritis is likely to be cell mediated. The C3H/He and C3H/HeJ ***mouse*** model provides an excellent opportunity to investigate the cellular basis of atrophic gastritis.

L3 ANSWER 6 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
4
AN 1997:227127 BIOSIS
DN PREV199799518843
TI Hyaluronate-CD44 interactions can induce murine B-cell activation.
AU Rafi, Asimah; Nagarkatti, Mitzi; Nagarkatti, Prakash S. (1)
CS (1) Dep. Biol., Virginia Polytechnic Inst. State Univ., Blacksburg, VA 24061 USA
SO Blood, (1997) Vol. 89, No. 8, pp. 2901-2908.
ISSN: 0006-4971.
DT Article
LA English
AB CD44 is a widely distributed cell surface glycoprotein whose principal ligand has been identified as hyaluronic acid (HA), a major component of the extracellular matrix (ECM). Recent studies have demonstrated that activation through CD44 leads to induction of effector function in T cells and macrophages. In the current study, we investigated whether HA or monoclonal antibodies (MoAbs) against CD44 would induce a proliferative response in ***mouse*** lymphocytes. Spleen cells from normal and nude, but not severe combined immunodeficient ***mice*** , exhibited strong proliferative responsiveness to stimulation with soluble HA or anti-CD44 MoAbs. Furthermore, purified B cells, but not T cells, were found to respond to HA. HA was unable to stimulate T cells even in the presence of antigen presenting cells (APC) and was unable to act as a costimulus in the presence of mitogenic or submitogenic concentrations of anti-CD3 MoAbs. in contrast, stimulation of B cells with HA in vitro, led to B-cell differentiation as measured by production of IgM antibodies in addition to increased expression of CD44 and decreased levels of CD45R. The fact that the B cells were responding directly to HA through its binding to CD44 and not to any contaminants or ***endotoxins*** was demonstrated by the fact that F(ab)-2 fragments of anti-CD44 MoAbs or soluble CD44 fusion proteins could significantly inhibit the HA-induced proliferation of B cells. Also, HA-induced proliferation of B cells was not affected by the addition of polymixin B, and B cells from lipopolysaccharide (LPS)- ***unresponsive*** C3H/HeJ strain responded strongly to stimulation with HA. Furthermore, HA, but not chondroitin-sulfate, another major component of the ECM, induced B-cell activation. It was also noted that injection of HA intraperitoneally, triggered splenic B cell proliferation in vivo. Together, the current study demonstrates that interaction between HA and CD44 can regulate murine B-cell effector functions and that such interactions may play a critical role during normal or autoimmune responsiveness of B cells.

L3 ANSWER 7 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 1997:173569 BIOSIS
DN PREV199799480172
TI Tumor necrosis factor-induced apoptosis during the poisoning of ***mice*** with hepatotoxins.
AU Leist, Marcel; Gantner, Florian; Naumann, Heike; Bluethmann, Horst; Vogt, Kathrin; Brigelius-Flohe, Regina; Nicotera, Pierluigi; Wolk, Hans-Dieter;

Wendel, Albrecht (1)
CS (1) Fac. Biol., Univ. Konstanz, P.O. Box 5560-M668, D-78434 Konstanz Germany
SO Gastroenterology, (1997) Vol. 112, No. 3, pp. 923-934.
ISSN: 0016-5085.
DT Article
LA English
AB Background & Aims: Treatment with tumor necrosis factor (TNF) induces murine hepatocyte apoptosis in vitro and in vivo when sensitizing concentrations of toxins are present. The aim of this study was to investigate whether endogenously formed TNF contributes to liver failure caused by hepatotoxins. Methods: The extent of liver damage, induced by alpha-amanitin or actinomycin D (ActD), was examined under various experimental conditions, preventing the action of TNF on hepatocytes. Results: TNF induced apoptosis of murine hepatocytes or human hepatoma cells in the presence of alpha-amanitin or ActD. TNF and alpha-amanitin induced such hepatotoxicity also in vivo in a synergistic way. After in vivo administration of high doses of ActD or alpha-amanitin alone, hepatic TNF-messenger RNA was increased and hepatocytes underwent apoptosis. A neutralizing antiserum against TNF-alpha prevented the liver injury. Hepatotoxicity of ActD or alpha-amanitin also was prevented by pretreatment of ***mice*** with low doses of the tolerizing cytokine interleukin 1. ***Mice*** deficient for the 55-kilodalton TNF receptor were protected from ActD- or alpha-amanitin-induced toxicity. ***Endotoxin*** - ***unresponsive*** C3H/HeJ ***mice*** also had liver failure after ActD treatment, and this damage was prevented by treatment with anti-TNF antiserum. Conclusions: Hepatotoxins such as alpha-amanitin may induce liver failure by an indirect mechanism involving sensitization of parenchymal cells toward endogenously produced TNF.

L3 ANSWER 8 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 1998:225812 BIOSIS
DN PREV199800225812
TI Sexual dimorphism in the ***mouse*** hypothalamic-pituitary-adrenal axis function after ***endotoxin*** and insulin stresses during development.
AU Spinedi, Eduardo (1); Chisari, Andrea; Pralong, Francois; Gaillard, Rolf C.
CS (1) IMBICE, Calle 526e/10 y 11, cc 403, 1900 La Plata Argentina
SO Neuroimmunomodulation, (***March-April, 1997***) Vol. 4, No. 2, pp. 77-83.
ISSN: 1021-7401.
DT Article
LA English
AB Bidirectional communication between the immune and the endocrine systems is now widely accepted as essential for the survival of the organism. Since a classical ***nonresponsive*** period of the hypothalamic-pituitary-adrenal (HPA) axis takes place shortly after birth and because endogenous sex hormones modulate immune function, the aim of the present work was to determine whether sex steroids regulate the PHA axis response to immune (bacterial, lipopolysaccharide, LPS) and nonimmune (insulin, INS) stressors in ***mice*** during development. For this purpose 7-, 15-, 30-, 45- and 60-day-old ***mice*** of both sexes were intraperitoneally injected with either vehicle alone (basal) or containing LPS (2 mg/kg body weight) or INS (12 IU/kg body weight). The animals were then killed by decapitation, 2 h or 45 min after LPS or INS, respectively. Plasma samples were assayed to measure corticosterone concentrations. The results indicated that: (a) there was a transient increase in basal plasma corticosterone levels during development, with a peak value at the juvenile age, regardless of sex; (b) a higher basal plasma corticosterone concentration in females than in males characterized the adult age; (c) the infantile age is a period of the HPA axis function ***nonresponsive*** to purely neuroendocrine but not to inflammatory stimuli; (d) during the juvenile age, females showed a hyporesponsive HPA axis to neuroendocrine and immune stress, whereas male ***mice*** were fully ***unresponsive*** to both challenges; (e) animals of both sexes showed a maximal HPA axis response to purely neuroendocrine stress at the prepubertal age; this response to the immune stimulus was also maximal in 30-day-old males, while it was found in females after puberty (45-day-old ***mice***); (f) sexual dimorphism in the HPA axis response to a purely neuroendocrine stimulus was found at 30 days of age or later, while this characteristic of the response to ***endotoxin*** was not present until puberty. These data clearly suggest that these are gender-dependent characteristics of the ontogeny of the HPA and HP-gonadal axes that are responsible for the sexual dimorphism of HPA axis function in ***mice*** .

L3 ANSWER 9 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1996:510494 BIOSIS
DN PREV199699232850
TI CD14 is a cell-activating receptor for bacterial ***peptidoglycan*** .
AU Gupta, Dipika,; Kirkland, Theo N.; Viriyakosol, Suganya; Dziarski, Roman (1)
CS (1) Northwest Cent. Med. Educ., Indiana Univ. Sch. Med., 3400 Broadway, Gary, IN 46408 USA
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 38, pp. 23310-23316.
ISSN: 0021-9258.
DT Article
LA English
AB The hypothesis that CD14 (an ***endotoxin*** receptor present on macrophages and neutrophils) acts as a cell-activating receptor for bacterial ***peptidoglycan*** was tested using ***mouse*** 70Z/3 cells transfected with human CD14. 70Z/3 cells transfected with an empty vector were ***unresponsive*** to insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of ***endotoxin*** . 70Z/3-CD14 cells were responsive to both insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of ***endotoxin*** , as measured by the expression of surface IgM, activation of NF-kappa-B, and degradation of I-kappa-B-alpha. ***Peptidoglycan*** also induced activation of NF-kappa-B and degradation of I-kappa-B-alpha in macrophage RAW264.7 cells. These ***peptidoglycan*** -induced effects (in contrast to ***endotoxin*** -induced effects) were not inhibited by polymyxin B. Both ***peptidoglycan*** - and ***endotoxin*** -induced activation of NF-kappa-B were inhibited by anti-CD14 mAb. The N-terminal 151 amino acids of CD14 were sufficient for acquisition of full responsiveness to both ***peptidoglycan*** and ***endotoxin*** , but CD14 deletion mutants lacking four small regions within the N-terminal 65 amino acids showed differentially diminished responses to ***peptidoglycan*** and ***endotoxin*** . These results identify CD14 as the functional receptor for ***peptidoglycan*** and demonstrate that similar, but not identical sequences in the N-terminal 65-amino acid region of CD14 are critical for the NF-kappa-B and IgM responses to both ***peptidoglycan*** and ***endotoxin*** .

L3 ANSWER 10 OF 106 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
DUPLICATE 8
AN 1995:206590 BIOSIS
DN PREV199598220890
TI Treponema pallidum and Borrelia burgdorferi lipoproteins and synthetic lipopeptides activate monocytes/macrophages.
AU Radolf, Justin D.; Arndt, Leslie L.; Akins, Darrin R.; Curetty, Linda L.; Levi, Marilyn E.; Shen, Yuenan; Davis, Laurie S.; Norgard, Michael V. (1)
CS (1) Dep. Microbiol., Univ. Texas Southwestern Med. Center, 5323 Harry Hines Blvd., Dallas, TX 75235-9048 USA
SO Journal of Immunology, (1995) Vol. 154, No. 6, pp. 2866-2877.
ISSN: 0022-1767.
DT Article
LA English
AB The observation that the major membrane immunogens of the spirochetal pathogens Treponema pallidum and Borrelia burgdorferi are lipoproteins prompted studies to investigate macrophage activation by the 47-kDa ***lipoprotein*** of T. pallidum and the acylated outer surface protein A (OspA) of B. burgdorferi. Both lipoproteins induced the synthesis of biologically active TNF-alpha and chloramphenicol acetyltransferase in a murine macrophage cell line transfected with a chloramphenicol acetyltransferase reporter gene controlled by a TNF promoter (TB2 cells). Nonacylated forms of these polypeptides did not induce cell activation. Comparison between purified OspA and B. burgdorferi cellular lipids revealed that the former was the more potent inducer of TNF-alpha. Synthetic lipohexapeptides corresponding to the N-termini of the 47-kDa ***lipoprotein*** of T. pallidum and OspA also activated TB2 cells in a dose-dependent fashion, whereas the nonlipidated hexapeptides were without effect, further underscoring the importance of protein acylation to cell activation. Among several lines of evidence supporting that macrophage stimulation by LPS and lipopeptides proceeds via different mechanisms, the most notable was that lipopeptides activated peritoneal macrophages from LPS- ***nonresponsive*** C3H/Hej ***mice*** . The potential for spirochetal lipoproteins to function as general macrophage activators was demonstrated by the ability of the synthetic analogues to induce IL-1-beta, IL-6, and IL-12, in addition to TNF, in murine and/or human macrophages. Our findings indicate that spirochetal lipoproteins may be important immunomodulators in syphilis and Lyme disease and that the synthetic lipopeptides will be useful surrogates for studying immune mechanisms operative in the two spirochetal diseases.

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NEWS 13 Jul 22 USAN to be reloaded July 28, 2002;
saved answer sets no longer valid
NEWS 14 Jul 29 Enhanced polymer searching in REGISTRY
NEWS 15 Jul 30 NETFIRST to be removed from STN
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NEWS 18 Aug 08 NTIS has been reloaded and enhanced
NEWS 19 Aug 19 Aquatic Toxicity Information Retrieval (AQUIRE)
now available on STN
NEWS 20 Aug 19 IFIPAT, IFICDB, and IFIUDB have been reloaded
NEWS 21 Aug 19 The MEDLINE file segment of TOXCENTER has been reloaded
NEWS 22 Aug 26 Sequence searching in REGISTRY enhanced
NEWS 23 Sep 03 JAPIO has been reloaded and enhanced
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NEWS 26 Sep 16 CA Section Thesaurus available in CAPLUS and CA
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NEWS 34 Dec 02 TIBKAT will be removed from STN
NEWS 35 Dec 04 CSA files on STN
NEWS 36 Dec 17 PCTFULL now covers WP/PCT Applications from 1978 to date
NEWS 37 Dec 17 TOXCENTER enhanced with additional content
NEWS 38 Dec 17 Adis Clinical Trials Insight now available on STN
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L2 ANSWER 1 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
1
AN 2002:495637 BIOSIS
DN PREV200200495637
TI Toll-like receptor 4 (TLR4)-deficient murine macrophage cell line as an in vitro assay system to show TLR4-independent signaling of Bacteroides fragilis lipopolysaccharide.
AU Lorenz, Eva (1); Patel, Dhavalkumar D.; Hartung, Thomas; Schwartz, David A.
CS (1) Section of Molecular Medicine and Infectious Diseases, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC, 27157-1042: elorenz@wfubmc.edu USA
SO Infection and Immunity, (September, 2002) Vol. 70, No. 9, pp. 4892-4896. print.
ISSN: 0019-9567.
DT Article
LA English
AB Bacterial lipopolysaccharides (LPS) activate cells of innate immunity, such as macrophages, by stimulating signaling through toll-like receptor 4 (TLR4). We and others have hypothesized that LPS derived from different bacterial species may function through TLR4-independent mechanisms. To test this hypothesis, we have generated using a nonviral transformation procedure a bone marrow-derived macrophage cell line called 10ScNCr/23 from mouse strain C57BL/10ScNCr. This mouse strain has a deletion of the TLR4 locus, causing the mouse strain to be ***nonresponsive*** to stimulation by LPS from Escherichia coli while responding normally to other bacterial substrates, such as ***lipoteichoic*** ***acid*** (LTA) from Staphylococcus aureus, which signal TLR4 independently. Stimulation with LTA induces five- and sixfold increases in 10ScNCr/23 cell line tumor necrosis factor alpha and macrophage inflammatory protein-2 (MIP-2) secretion, but no increases in either cytokine were found when cells were stimulated with E. coli LPS. Bacteroides fragilis-derived LPS, however, can effectively stimulate MIP-2 expression in the absence of functional TLR4 in the 10ScNCr/23 cell line. This gives rise to the notion that LPS from some bacterial species will utilize alternative receptors to stimulate the innate immune response.

L2 ANSWER 2 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
2
AN 2002:442102 BIOSIS
DN PREV200200442102
TI Hyporesponsiveness to vaccination with Borrelia burgdorferi OspA in humans and in TLR1- and TLR2-deficient mice.
AU Alexopoulou, Lena; Thomas, Venetta; Schnare, Markus; Lobet, Yves; Anguita, Juan; Schoen, Robert T.; Medzhitov, Ruslan; Fikrig, Erol; Flavell, Richard A. (1)
CS (1) Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, CT: erol.fikrig@yale.edu, richard.flavell@yale.edu USA
SO Nature Medicine, (August, 2002) Vol. 8, No. 8, pp. 878-884. http://www.nature.com/nm/. print.
ISSN: 1078-8956.
DT Article
LA English
AB The Lyme disease vaccine is based on the outer-surface lipoprotein (OspA) of the pathogen Borrelia burgdorferi, and 95% of vaccine recipients develop substantial titers of antibodies against OspA. Here, we identified seven individuals with very low antibody titers after vaccination (low responders). The macrophages of low responders produced less tumor necrosis factor-alpha and interleukin-6 after OspA stimulation and had lower cell-surface expression of Toll-like receptor (TLR) 1 as compared to normal cells, but normal expression of TLR2. TLRs activate innate responses to pathogens, and TLR2 recognizes lipoproteins and ***peptidoglycan*** (PGN). After OspA immunization, mice genetically deficient in either TLR2 (TLR2-/-) or TLR1 (TLR1-/-) produced low titers of antibodies against OspA. Notably, macrophages from TLR2-/- mice were ***unresponsive*** to OspA and PGN, whereas those from TLR1-/- mice responded normally to PGN but not to OspA. These data indicate that TLR1 and TLR2 are required for lipoprotein recognition and that defects in the TLR1/2 signaling pathway may account for human hyporesponsiveness to OspA vaccination.

L2 ANSWER 3 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2002:519337 BIOSIS
DN PREV200200519337
TI Intestinal epithelial cells (IEC) are broadly ***unresponsive*** to toll-like receptor (TLR)2-dependent bacterial ligands.
AU Melmed, Gil (1); Thomas, Lisa (1); Lee, Nahee (1); Michelsen, Kathrin (1); Zhou, Yuehua (1); Hu, Bing (1); Arditi, Moshe (1); Abreu, Maria T. (1)
CS (1) Los Angeles, CA USA
SO Gastroenterology, (April, 2002) Vol. 122, No. 4 Suppl. 1, pp. A-271. http://www.gastrojournal.org/. print.
Meeting Info.: Digestive Disease Week and the 103rd Annual Meeting of the American Gastroenterological Association San Francisco, CA, USA May 19-22, 2002
ISSN: 0016-5085.
DT Conference
LA English

L2 ANSWER 4 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
AN 2001048848 EMBASE
TI MD-2 enables Toll-like receptor 2 (TLR2)-mediated responses to lipopolysaccharide and enhances TLR2-mediated responses to gram-positive and gram-negative bacteria and their cell wall components.
AU Dziarski R.; Wang Q.; Miyake K.; Kirschning C.J.; Gupta D.

CS Dr. R. Dziarski, Indiana Univ. Sch. of Med., 3400 Broadway, Gary, IN 46408, United States. rdziar@iun.edu
SO Journal of Immunology, (1 Feb 2001) 166/3 (1938-1944).
Refs: 29
ISSN: 0022-1767 CODEN: JOIMA3
CY United States
DT Journal; Article
FS 004 Microbiology
026 Immunology, Serology and Transplantation
LA English
SL English
AB MD-2 is associated with Toll-like receptor 4 (TLR4) on the cell surface and enables TLR4 to respond to LPS. We tested whether MD-2 enhances or enables the responses of both TLR2 and TLR4 to Gram-negative and Gram-positive bacteria and their components. TLR2 without MD-2 did not efficiently respond to highly purified LPS and LPS partial structures. MD-2 enabled TLR2 to respond to nonactivating protein-free LPS, LPS mutants, or lipid A and enhanced TLR2-mediated responses to both Gram-negative and Gram-positive bacteria and their LPS, ***peptidoglycan*** , and ***lipoteichoic*** ***acid*** components. MD-2 enabled TLR4 to respond to a wide variety of LPS partial structures, Gram-negative bacteria, and Gram-positive ***lipoteichoic*** ***acid*** , but not to Gram-positive bacteria, ***peptidoglycan*** , and lipopeptide. MD-2 physically associated with TLR2, but this association was weaker than with TLR4. MD-2 enhanced expression of both TLR2 and TLR4, and TLR2 and TLR4 enhanced expression of MD-2. Thus, MD-2 enables both TLR4 and TLR2 to respond with high sensitivity to a broad range of LPS structures and to ***lipoteichoic*** ***acid*** , and, moreover, MD-2 enhances the responses of TLR2 to Gram-positive bacteria and ***peptidoglycan*** , to which the TLR4-MD-2 complex is ***unresponsive*** .

L2 ANSWER 5 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 2001:410217 BIOSIS
DN PREV200100410217
TI Discrimination of bacterial lipoproteins by toll-like receptor 6.
AU Takeuchi, Osamu; Kawai, Taro; Muehlradt, Peter F.; Morr, Michael; Radolf, Justin D.; Zychlinsky, Arturo; Takeda, Kiyoshi; Akira, Shizuo (1)
CS (1) Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, 3-1 Yamada-oka, Suita, Osaka, 565-0871 Japan
SO International Immunology, (July, 2001) Vol. 13, No. 7, pp. 933-940. print.
ISSN: 0953-8178.
DT Article
LA English
SL English
AB Bacterial lipoproteins (BLP) trigger immune responses via Toll-like receptor 2 (TLR2) and their immunostimulatory properties are attributed to the presence of a lipoylated N-terminus. Most BLP are triacylated at the N-terminus cysteine residue, but mycoplasmal ***macrophage*** - ***activating*** ***lipopeptide*** -2 kD (MALP-2) is only diacylated. Here we show that TLR6-deficient (TLR6-/-) cells are ***unresponsive*** to MALP-2 but retain their normal responses to lipopeptides of other bacterial origins. Reconstitution experiments in TLR2-/- TLR6-/- embryonic fibroblasts reveal that co-expression of TLR2 and TLR6 is absolutely required for MALP-2 responsiveness. Taken together, these results show that TLR6 recognizes MALP-2 cooperatively with TLR2, and appears to discriminate between the N-terminal lipoylated structures of MALP-2 and lipopeptides derived from other bacteria.

L2 ANSWER 6 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 2001:267916 BIOSIS
DN PREV200100267916
TI Functional cooperation of toll-like receptor 2 (TLR2) and TLR6 in human dermal endothelial cell (HMEC) activation by phenol soluble modulin (PSM). Role of tollip in TLR2 and TLR4 signaling.
AU Bulut, Yonca (1); Faure, Emmanuelle (1); Thomas, Lisa (1); Equils, Ozlem (1); Arditi, Moshe (1)
CS (1) Cedars-Sinai Medical Center, 8700 Beverly Blvd., Los Angeles, CA, 90048 USA
SO FASEB Journal, (March 7, 2001) Vol. 15, No. 4, pp. A649. print.
Meeting Info.: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638.
DT Conference
LA English
SL English
AB Background: Nine mammalian TLRs have been cloned to date. TLR2 mediates responses to ***peptidoglycan*** and lipopeptides from a variety of microbes, whereas TLR4 is the essential signaling receptor for LPS. Aims: 1- To elucidate the cooperative role of TLR2 and TLR6 in cellular responses to PSM, a peptide secreted by Staphylococcus epidermidis, and a TLR2 ligand. 2- To elucidate the role of Tollip, a newly discovered signaling molecule involved in IL-1R signaling, in TLR4 and TLR2-induced NF-kB activation. 3- To delineate the intracellular signaling molecules involved in TLR2-induced activation of NF-kB. Methods: mRNA expression of TLR2, TLR4 and TLR6 in HMEC by RT-PCR; transient transfection of ELAM-NF-kB-luciferase, wild type TLR2, TLR6 or Tollip or dominant negative (DN)TLR2, DN-TLR6, DN-MyD88, DN-IRAK, DN-TRAF6, DN-NIK and DN TRAF2 constructs; NF-kB luciferase and beta-galactosidase assays. Results: 1) HMEC express strongly TLR6 and TLR4 but not TLR2 mRNA by RT-PCR, and are ***unresponsive*** to PSM (50-200 ng/ml). 2) TLR2, but not TLR6 transfection is sufficient to restore the responsiveness of HMEC to PSM (NF-kB activation). 3)Co-transfection of DN-TLR2 or DN-TLR6 are both able to block PSM-induced NF-kB activation in TLR2-HMEC. 4) Overexpression of Tollip (0.1-0.5 mcg of cDNA) impairs (in a dose-dependent manner) NF-kB activation in response to LPS-TLR4 signaling in HMEC, and PSM-TLR2 signaling in TLR2-HMEC, as well as IL-1-induced signaling. 5) PSM-TLR2-induced NF-kB activation in TLR2- HMEC is inhibited by the DN constructs of MyD88, IRAK, TRAF6 and NIK but not TRAF2. Conclusions: PSM, a bacterial peptide and a TLR2 ligand, utilizes both TLR2 and TLR6, which work cooperatively to activate NF-kB in HMEC. Tollip is also an important constituent of the TLR4 and TLR2 signaling. PSM-TLR2/TLR6-induced NF-kB activation pathway shares the IL-1R signaling molecules, i.e. MyD88, IRAK and TRAF-6.

L2 ANSWER 7 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 2000:493319 CAPLUS
DN 133:101728
TI TLR2 and MyD88 gene knockout mouse as bacterial cell wall component-***unresponsive*** animal model
IN Akira, Shizuo; Takeuchi, Osamu; Takeda, Kiyoshi
PA Japan Science and Technology Corporation, Japan
SO PCT Int. Appl., 95 pp.
CODEN: PIXXD2
DT Patent
LA Japanese
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 2000041561	A1	20000720	WO 2000-JP132	20000113
W: AU, CA, JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1142472	A1	20011010	EP 2000-900372	20000113
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRAI JP 1999-7365 A 19990114
JP 1999-228282 A 19990812
JP 1999-309238 A 19991029
WO 2000-JP132 W 20000113
AB A TLR2 and MyD88 gene knockout mouse ***unresponsive*** to bacterial cell wall components such as peptidoglycans, lipoproteins, lipopeptides, endotoxin, ***lipoteichoic*** ***acid*** (LTA) Mycobacterium tuberculosis lysate, etc., useful in clarifying the role of each member of the TLR family (in particular, TLR2 and MyD88) in the signal transduction due to stimulation with bacterial cell components in vivo, is disclosed. This knockout mouse is prepd. by the homologous recombination method with the use of a targeting vector constructed by substituting the whole gene fragment or a part thereof of the exon site contg. the intracellular region of TLR2 or MyD88 gene by a plasmid having poly(A) signal and a marker gene. Also claimed is a screening method for bacterial component responsiveness regulators based on measuring the activation of macrophage or spleen cells, macrophage cytokine or nitrous acid ion prodn., or spleen cell MHC class II expression. More specifically, TLR2 (ant)agonists, interleukin-1 regulators, interleukin-18 regulators, or IFN-.gamma. regulators, or TNF-.alpha. regulators are screened. Lipoproteins/lipopeptides are derived from mycoplasma, Spirochaeta, or Escherichia genus.
RE.CNT 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L2 ANSWER 8 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 2000:758309 CAPLUS
DN 134:339203
TI Generation and analysis of endotoxin hypo-responsive knockout mice
AU Akira, Shizuo
CS Research Institute for Microbial Diseases, Osaka University, Osaka, Suita, Yamadaoka, 565-0871, Japan
SO Ensho (2000), 20(5), 589-594
CODEN: ENSHEE; ISSN: 0389-4290
PB Nippon Ensho Gakkai Jimukyoku
DT Journal; General Review
LA Japanese
AB A review with 19 refs. Toll in Drosophila is a receptor that is required for dorso-ventral polarity during development, and also involved in host defense against fungal infection. Recently, mammalian homolog of Toll, designated as Toll-like receptors (TLRs) have been identified. The TLR family harbors an extracellular leucine-rich repeat (LRR) domain and a cytoplasmic domain that is homologous to that of the IL-1R family. Analogous to the IL-1R, TLR recruits IRAK via adaptor MyD88, and then induces activation of TRAF6, NIK and finally NF-.kappa.B. In order to examine the role of TLR family, the authors have generated mice lacking TLR2, TLR4, and MyD88. TLR4 KO mice are hypo-responsive to LPS. On the other hand, TLR2 KO mice are hypo-responsive to ***peptidoglycan*** from gram-pos. bacteria, but not to LPS. MyD88 KO mice are ***unresponsive*** to LPS. Taken together, these results demonstrate that responses to bacterial cell wall components are differentially

mediated by TLR2 and TLR4, and that LPS signaling is mediated by TLR4 via MyD88.

L2 ANSWER 9 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
5
AN 2000:28195 BIOSIS
DN PREV200000028195
TI Function of CD14 as a ***peptidoglycan*** receptor: Differences and similarities with LPS.
AU Dziarski, Roman (1); Gupta, Dipika
CS (1) Northwest Center for Medical Education, Indiana University School of Medicine, Gary, IN, 46408 USA
SO Journal of Endotoxin Research, (1999) Vol. 5, No. 1-2, pp. 56-61. ISSN: 0968-0519.
DT General Review
LA English
SL English
AB ***Peptidoglycan*** (PGN) is a macrophage activator from Gram-positive bacteria. PGN activates cells of hemopoietic origin through CD14 since: (i) PGN- ***unresponsive*** CD14-negative cells become PGN-responsive after transfection with CD14 and expression of membrane CD14; (ii) PGN binds to CD14 with high affinity; and (iii) anti-CD14 mAbs inhibit both binding of PGN to CD14 and activation of CD14-positive cells by PGN. However, there are several differences in the function of CD14 as PGN and LPS receptor: (i) the kinetics of binding are different; (ii) the affinity of binding in the absence of LPS-binding protein (LBP) is higher for PGN than LPS; (iii) LBP does not increase the affinity of binding of PGN to CD14 and does not enhance cell activation by PGN (in contrast to LPS); (iv) the regions of CD14 needed for binding and activation are partially similar and partially different for PGN and LPS; (v) sCD14:PGN complexes, in contrast to sCD14:LPS complexes, do not activate CD14-negative cells; (vi) PGN, in contrast to LPS, does not activate CHO cells expressing mCD14; and (vii) PGN and LPS induce differential activation of MAP kinases, but activate similar transcription factors (NF-kappaB, ATF1/CREB, and AP-1).

L2 ANSWER 10 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
6
AN 1998:303727 BIOSIS
DN PREV199800303727
TI Endothelial and epithelial cells do not response to complexes of ***peptidoglycan*** with soluble CD14 but are activated indirectly by ***peptidoglycan*** -induced tumor necrosis factor-alpha and interleukin-1 from monocytes.
AU Jin, Yiping; Gupta, Dipika; Dziarski, Roman (1)
CS (1) Northwest Center Med. Education, Indiana Univ. Sch. Med., 3400 Broadway, Gary, IN 46408 USA
SO Journal of Infectious Diseases, (June, 1998) Vol. 177, No. 6, pp. 1629-1638. ISSN: 0022-1899.
DT Article
LA English
AB ***Peptidoglycan*** (PGN) activates macrophages through membrane CD14 (an endotoxin receptor) and binds to both soluble and membrane CD14. Since soluble CD14-lipopolysaccharide (LPS) complexes activate CD14-negative endothelial and epithelial cells, this study tested whether soluble CD14-PGN complexes activate human umbilical vein endothelial cells and epithelial-like U373 cells to secrete interleukin (IL)-6, express vascular cellular adhesion molecule-1, and translocate nuclear factor-kappaB. In contrast to LPS, endothelial, epithelial, and other cells of non-hemopoietic origin were ***unresponsive*** to PGN through soluble or membrane-bound CD14, whereas cells of hemopoietic origin were responsive to both PGN and LPS. PGN, similarly to LPS, activated endothelial and epithelial cells indirectly in the presence of 2%-4% blood, by inducing secretion of both tumor necrosis factor-alpha and IL-1 from monocytes. These results reveal different mechanisms of CD14 function and cell activation for LPS and PGN and also demonstrate strong indirect activation of endothelial and epithelial cells by both PGN and LPS.

L2 ANSWER 11 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
7
AN 1996:510494 BIOSIS
DN PREV199699232850
TI CD14 is a cell-activating receptor for bacterial ***peptidoglycan*** .
AU Gupta, Dipika,; Kirkland, Theo N.; Viriyakosol, Suganya; Dziarski, Roman (1)
CS (1) Northwest Cent. Med. Educ., Indiana Univ. Sch. Med., 3400 Broadway, Gary, IN 46408 USA
SO Journal of Biological Chemistry, (1996) Vol. 271, No. 38, pp. 23310-23316. ISSN: 0021-9258.
DT Article
LA English
AB The hypothesis that CD14 (an endotoxin receptor present on macrophages and neutrophils) acts as a cell-activating receptor for bacterial ***peptidoglycan*** was tested using mouse 70Z/3 cells transfected with human CD14. 70Z/3 cells transfected with an empty vector were ***unresponsive*** to insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of endotoxin. 70Z/3-CD14 cells were responsive to both insoluble and soluble ***peptidoglycan*** , as well as to low concentrations of endotoxin, as measured by the expression of surface IgM, activation of NF-kappa-B, and degradation of I-kappa-B-alpha. ***Peptidoglycan*** also induced activation of NF-kappa-B and degradation of I-kappa-B-alpha in macrophage RAW264.7 cells. These ***peptidoglycan*** -induced effects (in contrast to endotoxin-induced effects) were not inhibited by polymyxin B. Both ***peptidoglycan*** - and endotoxin-induced activation of NF-kappa-B were inhibited by anti-CD14 mAb. The N-terminal 151 amino acids of CD14 were sufficient for acquisition of full responsiveness to both ***peptidoglycan*** and endotoxin, but CD14 deletion mutants lacking four small regions within the N-terminal 65 amino acids showed differentially diminished responses to ***peptidoglycan*** and endotoxin. These results identify CD14 as the functional receptor for ***peptidoglycan*** and demonstrate that similar, but not identical sequences in the N-terminal 65-amino acid region of CD14 are critical for the NF-kappa-B and IgM responses to both ***peptidoglycan*** and endotoxin.

L2 ANSWER 12 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
8
AN 1996:464138 BIOSIS
DN PREV199699186494
TI Tolerance to appetite suppression induced by ***peptidoglycan*** .
AU Biberstine, Karla J.; Darr, David S.; Rosenthal, Raoul S. (1)
CS (1) Dep. Microbiol. Immunol., Indiana Univ. Sch. Med., 635 Barnhill Dr., Indianapolis, IN 46202 USA
SO Infection and Immunity, (1996) Vol. 64, No. 9, pp. 3641-3645. ISSN: 0019-9567.
DT Article
LA English
AB Physiologically realistic ***peptidoglycan*** (PG) fragments, derived from Neisseria gonorrhoeae, were shown previously to dose-dependently suppress food consumption and body weight gain in rats following single intraperitoneal injections. The present study, examining the effects of repeated daily injection of PG, provides additional support to our underlying hypothesis, i.e., that soluble PG fragments contribute to the loss of appetite commonly associated with bacterial infections. An initial intraperitoneal injection of purified, soluble, macromolecular, extensively O-acetylated PG fragments (S-O-PG) (240 mu-g/kg of body weight) decreased overnight food consumption in male Lewis rats (150 g) by approximately 35% relative to animals receiving diluent alone (P lt 0.05). However, subsequent daily injections of S-O-PG resulted in progressively smaller effects on food consumption until, by the fourth day, rats were completely ***nonresponsive*** (tolerant) to S-O-PG-induced hypophagia. Rats that developed tolerance to the effects of S-O-PG on appetite were also tolerant to three other known hypophagic agents, lipopolysaccharide (LPS), muramyl dipeptide, and interleukin-1, when challenged one day after establishment of S-O-PG tolerance. Similarly, rats developed tolerance to repeated injections of muramyl dipeptide or LPS and were cross-tolerant to S-O-PG when challenged 1 day later. However, 30 days after establishment of S-O-PG tolerance, rats remained ***nonresponsive*** to S-O-PG but regained full responsiveness to LPS-mediated hypophagia. Thus, at least two mechanisms of tolerance to S-O-PG hypophagia exist: an early tolerance which is nonspecific and a late tolerance which is specific for S-O-PG. Late, but not early, tolerance to S-O-PG-mediated suppression of appetite was associated with an increase in specific anti-PG antibody activity as measured in an enzyme-linked immunosorbent assay.

L2 ANSWER 13 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
9
AN 1993:320303 BIOSIS
DN PREV199396028653
TI Induction of macrophage-mediated production of tumor necrosis factor alpha by an L-form derived from Staphylococcus aureus.
AU Kuwano, Koichi; Akashi, Akira; Matsu-Ura, Ikuko; Nishimoto, Mitsunobu; Arai, Sumio (1)
CS (1) Dep. Microbiol., Kurume Univ. Sch. Med., 67 Asahi-machi, Kurume 830 Japan
SO Infection and Immunity, (1993) Vol. 61, No. 5, pp. 1700-1706. ISSN: 0019-9567.
DT Article
LA English
AB We investigated the capability of an L-form derived form Staphylococcus aureus to induce tumor necrosis factor alpha (TNF-alpha) production in murine peritoneal macrophages. The activity for TNF-alpha induction was found in the membrane fraction of the L-form but not in the cytoplasmal fraction purified by the sucrose step gradient centrifugation. TNF-alpha mRNA was also detected in macrophages stimulated with L-form membranes. L-form induced TNF-alpha production in macrophages from both lipopolysaccharide-responsive and - ***unresponsive*** mouse strains. Regardless of the presence of polymyxin B, the activity of TNF-alpha induction of L-form was mostly found in the phenol layer, but not in the aqueous layer, both of which were prepared by phenol extraction method. Fractions of L-form membranes representing molecular mass of approximately between 29 and 36 kDa were primarily responsible for inducing the production of TNF-alpha consistently. Moreover, this stimulatory effect was abolished by digestion with Streptomyces griseus protease. In Western blot (immunoblot) analysis with anti- ***lipoteichoic*** ***acid*** antibody, two bands (65 and 45 kDa) were observed in the sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the phenol layer, whereas

one band (14 kDa) was observed in either the aqueous layer or ***lipoteichoic*** ***acid*** of S. aureus. These results suggest that the component in the membrane of the L-form, distinct from cell wall components such as teichoic acid or lipopolysaccharide, possesses the capability to stimulate TNF-alpha production by macrophages.

L2 ANSWER 14 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
10
AN 1993:75144 BIOSIS
DN PREV199395039644
TI In vitro induction of cecropin genes: An immune response in a Drosophila blood cell line.
AU Samakovlis, Christos; Asling, Bengt; Boman, Hans G.; Gateff, Elisabeth; Hultmark, Dan (1)
CS (1) Dep. Mol. Biol., Stockholm Univ., S-106 91 Stockholm Sweden
SO Biochemical and Biophysical Research Communications, (1992) Vol. 188, No. 3, pp. 1169-1175.
ISSN: 0006-291X.
DT Article
LA English
AB The Drosophila melanogaster cell line mbn-2 was explored as a model system to study insect immune response in vitro. This cell line is of blood cell origin, derived from larval hemocytes of the mutant lethal (2) malignant blood neoplasm (l(2)mbn). The mbn-2 cells respond to microbial substances by the activation of cecropin genes, coding for bactericidal peptides. The response is stronger than that previously described for SL2 cells, and four other tested Drosophila cell lines were totally ***unresponsive*** . Bacterial lipopolysaccharide, algal laminarin (a beta-1,3-glucan), and bacterial flagellin were strong inducers, bacterial ***peptidoglycan*** fragments gave a weaker response, whereas a formyl-methionine-containing peptide had no effect. Experiments with different drugs indicate that the response may be mediated by a G protein, but not by protein kinase C or eicosanoids, and that it requires a protein factor with a high rate of turnover.

L2 ANSWER 15 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AN 88040520 EMBASE
DN 1988040520
TI Adherence of Streptococcus agalactiae to synchronously growing human cell monolayers without ***lipoteichoic*** ***acid*** involvement.
AU Miyazaki S.; Leon O.; Panos C.
CS Department of Microbiology, Jefferson Medical College, Thomas Jefferson University, Philadelphia, PA 19107, United States
SO Infection and Immunity, (1988) 56/2 (505-512).
ISSN: 0019-9567 CODEN: INFIBR
CY United States
DT Journal
FS 004 Microbiology
LA English
SL English
AB Freshly isolated virulent and nonvirulent strains of Streptococcus agalactiae type III were used to study differences in coccal adherence to synchronously dividing, subconfluent human embryonic amnion and fetal lung monolayers in vitro. The adherence frequency by virulent isolates of mid-logarithmically growing cocci to amnion cells varied markedly with host cell age, being highest shortly after eucaryotic cell division. This variation was not observed with lung cell monolayers, suggesting that cyclic production or exposure of coccal receptor sites on the eucaryotic cell surface with age is not a common property of all primary human cells in vitro. However, and regardless of age, not all cells within these synchronously dividing populations bound virulent cocci, indicating that a very small segment of a population may always be ***unresponsive*** to host cell interactions with a cocal pathogen. By comparison, adherence of nonvirulent coccal isolates to amnion and lung cells remained constant and of a very low order, regardless of host cell age. Maximal adherence of virulent S. agalactiae to young host cells occurred at early and mid-logarithmic phases of growth. However, at the late stationary growth phase, adherence was reduced to almost that of nonvirulent isolates. Pretreatment of virulent S. agalactiae with anti- ***lipoteichoic*** ***acid*** (LTA) serum failed to inhibit coccal adherence to these different host cells. Heat negated adherence. Group B coccal LTA was cytotoxic for these host cells. However, pretreatment of amnion and lung cells with nontoxic levels of this amphiphile did not prevent attachment of virulent cocci. Finally, coccal pretreatment with pronase abrogated adherence to either host cell even though surface-exposed LTA was uneffected, as observed by the indirect fluorescent-antibody procedure. Likewise, no observable difference in surface LTA was detected when fresh isolates of virulent and nonvirulent coccal strains were compared by this procedure. These studies suggest that protein involvement, rather than LTA, is primarily responsible for mediating virulent S. agalactiae type III attachment to these synchronously growing, subconfluent eucaryotic monolayers in vitro.

L2 ANSWER 16 OF 19 CAPLUS COPYRIGHT 2003 ACS
AN 1985:404817 CAPLUS
DN 103:4817
TI ***Peptidoglycan*** from the potentially pathogenic oral bacterium Actinomyces viscosus is a B-cell mitogen
AU Baker, J. J.
CS Sch. Dent. Med., Univ Pittsburgh, Pittsburgh, PA, 15261, USA
SO Archives of Oral Biology (1985), 30(3), 291-4
CODEN: AOBIAR; ISSN: 0003-9969
DT Journal
LA English
AB Cell walls and ***peptidoglycan*** from A. viscosus, strain M-100 were compared for their ability to act as mitogens with spleen cells from germ-free Fischer rats. The cell walls were prepd. from trypticase soy broth grown whole cells using a French press, followed by 2 consecutive washes with 0.1 M Tris-HCl buffer, pH 8.0, 1 M NaCl, and distd. water. ***Peptidoglycan*** was prepd. from cell walls by 3 consecutive formamide extns. at 165.degree.. On a dry-wt. basis, the ***peptidoglycan*** was a significantly better mitogen than cell walls, suggesting that the ***peptidoglycan*** is the major mitogenic component of A. viscosus cell walls. Mononuclear spleen cells were sepd. on a Nylon-wool column into a non-adherent subpopulation enriched for T lymphocytes and a weakly-adherent, plunger-removable subpopulation enriched for B lymphocytes. The non-adherent T-cell subpopulation responded strongly to the T-cell mitogen phytohemagglutinin (PHA) but was ***unresponsive*** to both the ***peptidoglycan*** and cell walls from A. viscosus. In contrast, the weakly-adherent enriched B-cell subpopulation was less responsive to PHA, but was strongly stimulated by A. viscosus ***peptidoglycan*** and cell walls. Thus, cell mitogen ***peptidoglycan*** and cell walls from A. viscosus are B-cell mitogens.

L2 ANSWER 17 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 11
AN 84019324 EMBASE
DN 1984019324
TI Induction of interleukin secretion by adjuvant-active peptidoglycans.
AU Vacheron F.; Guenounou M.; Nauciel C.
CS Laboratoire de Biochimie, Centre Universitaire Pharmaceutique, 92290 Chatenay-Malabry, France
SO Infection and Immunity, (1983) 42/3 (1049-1054).
CODEN: INFIBR
CY United States
DT Journal
FS 004 Microbiology
025 Hematology
026 Immunology, Serology and Transplantation
LA English
AB The ability of differently structured, purified peptidoglycans (PG) to induce interleukin 1 (IL1) secretion was compared. PG from Bacillus megaterium and Staphylococcus aureus stimulated the production of IL1 by mouse peritoneal macrophages in human adherent mononuclear cells, whereas PG from Micrococcus lysodeikticus and Corynebacterium poinsettiae were inactive. There was a correlation between the ability of PG to induce IL1 secretion and previously demonstrated immunoenhancing activities (adjuvant effect, increase of resistance to tumor growth) of PG. PG solubilization by lysozyme decreased but did not abolish the PG effect on IL1 secretion. Active PG induced IL1 production in nude mice and in the C3H/HeJ strain (which is ***unresponsive*** to lipopolysaccharides).

L2 ANSWER 18 OF 19 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE
12
AN 1983:284034 BIOSIS
DN BA76:41526
TI ENHANCEMENT OF MURINE IMMUNE RESPONSES TO ORALLY ADMINISTERED HAPTENATED
STREPTOCOCCUS-MUTANS.
AU KIYONO H; MICHALEK S M; MOSTELLER L M; TORII M; HAMADA S; MCGHEE J R
CS DEP. MICROBIOL., UNIV. ALABAMA BIRMINGHAM, UNIV. STN., BIRMINGHAM, ALA.
35294, U.S.A.
SO SCAND J IMMUNOL, (1982 (RECD 1983)) 16 (6), 455-464.
CODEN: SJIMAX. ISSN: 0300-9475.
FS BA; OLD
LA English
AB The induction of immune responses to orally administered trinitrophenyl (TNP)-haptenated S. mutans and its enhancement with muramyldipeptide (MDP), ***peptidoglycan*** (PG) and concanavalin A (Con A) were investigated in lipopolysaccharide (LPS)- ***nonresponsive*** C3H/HeJ mice and the syngeneic, LPS-responsive C3H/HeN strain. Both mouse strains manifested similar immune responses, primarily of the IgM isotype, after a single gastric intubation (GI) with TNP-S. mutans. When groups of animals were first carrier-primed by GI with S. mutans for 2 consecutive days, followed by a single GI with TNP-S. mutans 1 wk later, C3H/HeJ mice gave a significantly higher (P .ltoreq. 0.01) splenic IgA anti-TNP plaque-forming cell (PFC) response than identically treated C3H/HeN mice. Saliva, urine and serum from these C3H/HeJ mice possessed high levels of IgA anti-TNP antibodies as determined by the enzyme-linked immunosorbent assay, C3H/HeN
mice exhibited low antibody levels. Oral administration of Con A (either 250 .mu.g or 500 .mu.g/mouse) or purified PG [prostaglandin] (1 mg/mouse) at the time of TNP-S. mutans immunization resulted in significantly (P .ltoreq. 0.01) enhanced splenic IgA anti-TNP PFC responses, especially in C3H/HeJ mice. MDP promoted IgA anti-TNP PFC responses in LPS-responsive C3H/HeN mice but did not augment responses in C3H/HeJ animals. A similar immune response pattern was seen when antibody levels were measured in serum, saliva and urine of both mouse strains. These results demonstrate that haptenated S. mutans is a good antigen for the induction of high IgA responses in orally immunized C3H/HeJ mice and that this high response can be enhanced with the adjuvants Con A and PG. MDP is ineffective in C3H/HeJ mice but enhances IgA responses in normal LPS-responsive C3H/HeN animals.

L2 ANSWER 19 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 13
AN 83019418 EMBASE
DN 1983019418
TI Study of adjuvant and mitogenic activities of bacterial peptidoglycans with different structures.
AU Guenounou M.; Goguel A.F.; Nauciel C.
CS Lab. Biochim., UER Sci. Pharm. Biol., 92290 Chatenay-Malabry, France
SO Annales d'Immunologie, (1982) 133 D/1 (3-13).
CODEN: ANIMCZ
CY France
DT Journal
FS 037 Drug Literature Index
026 Immunology, Serology and Transplantation
004 Microbiology
022 Human Genetics
LA English
SL French
AB The adjuvant and mitogenic properties of bacterial peptidoglycans (PG) of different structures have been compared. The PG from Bacillus megaterium and Staphylococcus aureus were adjuvant-active in the guinea-pig, and mitogenic for guinea-pig and mouse lymphocytes. On the other hand the PG from Micrococcus lysodeikticus and Corynebacterium poinsettiae exerted neither adjuvant nor mitogenic activities. Mitogenic PG were selective B mitogens. They were mitogenic for splenocytes from nude mice and inactive towards T-cell-enriched populations. They were mitogenic in both germ-free mice and in the C3H/HeJ strain which is ***unresponsive*** to lipopolysaccharide.

=> s MALP 2
L3 56 MALP 2

=> dup rem l3
PROCESSING COMPLETED FOR L3
L4 27 DUP REM L3 (29 DUPLICATES REMOVED)

=> l4 and py<1999
L4 IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

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2 FILES SEARCHED...
L5 4 L4 AND PY<1999

=> dup rem l5
PROCESSING COMPLETED FOR L5
L6 4 DUP REM L5 (0 DUPLICATES REMOVED)

=> d bib abs 1-
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L6 ANSWER 1 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:31687 BIOSIS
DN PREV199900031687
TI A Mycoplasma fermentans-derived synthetic lipopeptide induces AP-1 and NF-kappaB activity and cytokine secretion in macrophages via the activation of mitogen-activated protein kinase pathways.
AU Garcia, Josefina; Lemercier, Brigitte; Roman-Roman, Sergio; Rawadi, Georges (1)
CS (1) Inst. Pasteur, Lab. Mycoplasmes, 25 rue Docteur Roux, 75724 Paris Cedex 1 France
SO Journal of Biological Chemistry, (***Dec. 18, 1998***) Vol. 273, No. 51, pp. 34391-34398.
ISSN: 0021-9258.
DT Article
LA English
AB Mycoplasma lipoproteins have been demonstrated to stimulate monocytic cells and induce proinflammatory cytokine secretion. In this paper, we show that a synthetic analog of the Mycoplasma fermentans membrane-associated lipopeptide macrophage-activating lipopeptide-2 (***MALP*** - ***2***) induces mRNA synthesis and protein secretion of interleukin-1beta and tumor necrosis factor-alpha in human monocytes/macrophages and the murine macrophage cell line RAW 264.7, whereas the nonlipidated counterpart lacks this effect, underscoring the importance of protein acylation for cell activation. Synthetic ***MALP*** - ***2*** (sMALP-2) induced the activation of MAPK family members extracellular signal regulated kinases 1 and 2, c-Jun NH2-terminal kinase, and p38 and induced NF-kappaB and AP-1 transactivation in macro. phages. Whereas the specific p38 inhibitor SB203580 abrogated both cytokine synthesis and NF-kappaB and AP-1 transactivation in response to ***MALP*** - ***2*** , the selective MAPK/extracellular signal-regulated kinase-1 inhibitor PD-98059 decreased interleukin-1beta and tumor necrosis factor-alpha production in response to sMALP-2 without affecting the transactivation of NF-kappaB or AP-1. These results indicate that activation of MAPKs by sMALP-2 is a crucial event leading to the expression of proinflammatory cytokines. Our findings demonstrate that the synthetic analog of ***MALP*** - ***2*** reproduces the macrophage stimulation activity found in different fractions of mycoplasmas. Given that ***MALP*** - ***2*** has been recently shown to be expressed at the surface of M. fermentans as a molecular entity, sMALP-2 constitutes a valuable surrogate for investigating immunomodulation by these microorganisms and evaluating the role that this activity plays in the development of inflammatory diseases associated with mycoplasma infections.

L6 ANSWER 2 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:480598 BIOSIS
DN PREV199800480598
TI Structure and specific activity of macrophage-stimulating lipopeptides from Myocoplasma hyorhinis.
AU Muehlradt, Peter F. (1); Kiess, Michael; Meyer, Holger; Suessmuth, Roderich; Jung, Guenther
CS (1) Immunobiol. Res. Group, Gesellschaft Biotechnol., Forschung m.b.H., Mascheroderweg 1, D-38124 Braunschweig Germany
SO Infection and Immunity, (***Oct., 1998***) Vol. 66, No. 10, pp. 4804-4810.
ISSN: 0019-9567.
DT Article
LA English
AB Mycoplasmas are potent macrophage stimulators. We describe the isolation of macrophage-stimulatory lipopeptides S-(2,3-bisacyl(C16:0/C18:0)oxypropyl)cysteinyl-GQTDNNSSQSQQPGSGTTNT and S-(2,3-bisacyl (C16:0/C18:0)oxypropyl) cysteinyl-GQTN derived from the Mycoplasma hyorhinis variable lipoproteins VlpA and VlpC, respectively. These lipopeptides were characterized by amino acid sequence and composition analysis and by mass spectrometry. The lipopeptides S-(2,3-bis(palmitoyloxy)propyl)cysteinyl-GQTNT and S-(2,3-bis(palmitoyloxy)propyl)cysteinyl-SKKKK and the N-palmitoylated derivative of the latter were synthesized, and their macrophage-stimulatory activities were compared in a nitric oxide release assay with peritoneal macrophages from C3H/HeJ mice. The lipopeptides with the free amino terminus showed half-maximal activity at 3 pM regardless of their amino acid sequence; i.e., they were as active as the previously isolated M. fermentans-derived lipopeptide ***MALP*** - ***2*** . The macrophage-stimulatory activity of the additionally N-palmitoylated lipopeptide or of the murein lipoprotein from Escherichia coli, however, was lower by orders of magnitude. It is concluded that the lack of N-acyl groups in mycoplasmal lipoproteins explains their exceptionally high in vitro macrophage-stimulatory capacity. Certain features that lipopolysaccharide endotoxin and mycoplasmal lipopeptides have in common are discussed. Lipoproteins and lipopeptides are likely to be the main causative agents of inflammatory reactions to mycoplasmas. This may be relevant in the context of mycoplasmas as arthritogenic pathogens and their association with AIDS.

L6 ANSWER 3 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1997:309117 BIOSIS
DN PREV199799616920
TI Isolation, structure elucidation, and synthesis of a macrophage stimulatory lipopeptide from Mycoplasma fermentans acting at picomolar concentration.
AU Muehlradt, Peter F. (1); Kiess, Michael; Meyer, Holger; Suessmuth, Roderich; Jung, Guenther
CS (1) Immunobiol. Res. Group, GBF, Mascheroderweg 1, D-38124 Braunschweig
Germany
SO Journal of Experimental Medicine, (1997) Vol. 185, No. 11, pp. 1951-1958.
ISSN: 0022-1007.
DT Article
LA English
AB Macrophages are typically stimulated by components of microbial cell walls. Surprisingly, cell wall-less mycoplasmas can also very efficiently stimulate macrophages. We showed recently that mycoplasma-derived lipopeptides constitute the active principle. We have now isolated a clone of Mycoplasma fermentans expressing mainly one macrophage-stimulating lipopeptide. This lipopeptide was detergent-extracted and isolated by reversed-phase high-performance liquid chromatography, using nitric oxide release from C3H/HeJ mouse macrophages as bioassay for detection. In contrast to "conventional" bacterial lipoproteins, this lipopeptide had a free NH-2 terminus. Amino acid composition, sequence, and the molecular weight of 2,163.3 are consistent with the following structure: S-(2,3-bisacyloxypropyl)cysteine-GNNDESNISFYEK with one mole C16:0, and a further mole of a mixture of C18:0 and C18:1 fatty acid per lipopeptide molecule. The sequence could not be found in either the protein identification resource nor the Swiss Prot data bank. We named this 2-kD lipopeptide, macrophage-activating lipopeptide-2 (***MALP*** - ***2***). Synthetic dipalmitoyl ***MALP*** - ***2*** and mycoplasma-derived ***MALP*** - ***2*** were compared with the bioassay. Both hypopeptides showed an identical dose dependency with a half-maximal response at 10-11 M concentration. ***MALP*** - ***2*** may be one of the most potent natural macrophage stimulators besides endotoxin.

L6 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:135942 BIOSIS
DN PREV199800135942
TI Cisovka: The relic population of Abies alba and its relationship to man-made silver-fir stands in Bialowieza Primeval Forest.

AU Mejnartowicz, Leon (1)
CS (1) Inst. Dendrol., Polish Acad. Sci., 62-035 Kornik Poland
SO Acta Societatis Botanicorum Poloniae, (1996) Vol. 65, No. 3-4, pp. 319-328.
ISSN: 0001-6977.
DT Article
LA English
SL English; Polish
AB In Bialowieza Primeval Forest, in 1823 Stanislaw Gorski discovered on the Cisovka Hag, a relic population of European silver-fir (Abies alba Mill.). This population is isolated and most away, 120 km to the North-East, from the border of European-silver-fir distribution. Besides the natural population Cisovka, there are also man-made silver fir stands and clumps in the Polish and Belorussian part of Bialowieza Primeval Forest. In the Polish part there are four such artificial stands. If the seed-producing silver-fir stands really originated from the Cisovka population, then they are a very valuable part of the declining population and an easy accessible seed source. However, if these populations were introduced to the Bialowieza Primeval Forest, then they are a potential source of dangerous genetic pollution of the Cisovka population. The relationship of the genetic structure of the Cisovka population to man-made silver-fir-stands in Bialowieza Forest was investigated with the help of 17 loci of 11 enzyme systems. Genetic diversity of Cisovka population is characterized by the smallest mean number of alleles per locus (Mal = 1.353, includes all loci studied and per polymorphic locus ***Malp*** = ***2*** .00). In Cisovka population there is very low-grade of polymorphic loci (Pp = 11.765 with the mean 37.255 for all studied populations). Expected heterozygosity, He = 0.079 revealed very low-grade of genetic diversity in the population. The observed heterozygosity (Ho = 0.123) was similar to this characteristic in other populations. A dendrogram based on Neis genetic distance coefficient (D) among 9 silver-fir populations was constructed. Cisovka in the UPGMA dendrogram is a distinct population separated from other ones by a very great genetic distance (D = 0.06). Also two man-made silver-fir (B1 and B2) stands are separated from others. Only populations B3 and B4 are combined into one subgroup linked to the population Tomaszow Lubelski. Basing on the received results one should decide that all the four studied artificial stands were introduced to Bialowieza Primeval Forest from beyond of this geographical regions. There is some reason to assume (on the GDH2 allele frequency) that man-made silver-stands in compartments 453Aa and 498Cg are of eastern provenance. It is rather certain that these stands are not of offspring of Cisovka populations.

=> d his

(FILE 'HOME' ENTERED AT 16:21:18 ON 06 JAN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 16:21:34 ON 06 JAN 2003
L1 42 S (PEPTIDOGLYCAN OR MACROPHAGE ACTIVATING LIPOPEPTIDE OR LIPOTE
L2 19 DUP REM L1 (23 DUPLICATES REMOVED)
L3 56 S MALP 2
L4 27 DUP REM L3 (29 DUPLICATES REMOVED)
L5 4 S L4 AND PY<1999
L6 4 DUP REM L5 (0 DUPLICATES REMOVED)

=> s lipoteichoic acid
L7 2638 LIPOTEICHOIC ACID

=> s l7 and (immun? or vaccin? or adjuvant?)
L8 969 L7 AND (IMMUN? OR VACCIN? OR ADJUVANT?)

=> s l8 and py<1999
2 FILES SEARCHED...
L9 596 L8 AND PY<1999

=> d bib abs 1-10

L9 ANSWER 1 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:146061 BIOSIS
DN PREV199900146061
TI Interactions between ***lipoteichoic*** ***acid*** and lipopolysaccharide on human lung microvascular endothelial cell adhesion molecule expression and interleukin-8 release.
AU Blease, Kate (1); Chen, Yan; Hellewell, Paul G.; Burke-Gaffney, Anne (1)
CS (1) Leukocyte Biol., BMS Div., NHLI Div., Imperial Coll. Sch. Med., London UK
SO British Journal of Pharmacology, (***Dec., 1998***) Vol. 125, No. PROC. SUPPL., pp. 31P.
Meeting Info.: Joint Meeting of the British Pharmacological Society and the Physiological Society Southampton, England, UK September 8-11, 1998
ISSN: 0007-1188.
DT Conference
LA English

L9 ANSWER 2 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:130202 BIOSIS
DN PREV199900130202
TI Identification of genes involved in innate responsiveness to bacterial products by differential display.
AU Jin, Fenyu; Nathan, Carl; Ding, Aihao (1)
CS (1) Cornell Univ. Med. Coll., Box 57, 1300 York Ave., Room A-225, New York, NY 10021 USA
SO Methods (Orlando), (***Dec., 1998***) Vol. 16, No. 4, pp. 396-406.
ISSN: 1046-2023.
DT Article
LA English
AB To explore gene regulation by bacterial lipopolysaccharide (LPS), we compared mRNA profiles of macrophage cell lines from two strains of mice congenic for a locus markedly affecting their ability to respond to LPS. Differential display detected four differentially expressed transcripts. One transcript encoded the mouse homolog of human secretory leukocyte protease inhibitor (SLPI), which was expressed by LPS-hyporesponsive macrophage cells (Lpsd) but not by LPS-normoresponsive cells (LpSn). Among five macrophage cell lines, secretion of SLPI was inversely correlated with ability to produce nitric oxide (NO) and tumor necrosis factor alpha in response to LPS. Stable transfection of LPS-responsive macrophages with SLPI suppressed LPS-induced responses. Interferon-gamma (IFN-gamma), which corrects the defective LPS response in Lpsd macrophages, suppressed the LPS-induced expression of SLPI and restored LPS response to SLPI-overexpressing macrophages. Besides its role as a LPS response inhibitor, mouse SLPI is also a ***lipoteichoic*** ***acid*** response inhibitor. The expression of SLPI was strongly enhanced by interleukin-10 and -6. SLPI may be an important antiinflammatory molecule in host defense against gram-negative and gram-positive bacteria.

L9 ANSWER 3 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:75034 BIOSIS
DN PREV199900075034
TI A ***lipoteichoic*** ***acid*** fraction of Enterococcus hirae activates cultured human monocytic cells via a CD14-independent pathway to promote cytokine production, and the activity is inhibited by serum components.
AU Arakaki, Rieko; Sugawara, Shunji; Nakashima, Hideki; Kotani, Shozo; Takada, Haruhiko (1)
CS (1) Dep. Microbiol. Immunol., Kagoshima Univ. Dent. Sch., Kagoshima 890-8544 Japan
SO FEMS Immunology and Medical Microbiology, (***Dec., 1998***) Vol. 22, No. 4, pp. 283-291.
ISSN: 0928-8244.
DT Article
LA English
AB To elucidate the cellular activation mechanisms of ***lipoteichoic*** ***acid*** (LTA) compared with those of lipopolysaccharide (LPS), a quantitatively major LTA fraction, QM-1M, was prepared from hot phenol-water extracts of Enterococcus hirae (ATCC 9790) by hydrophobic octyl-Sepharose chromatography and by ion-exchange membrane (QMA-Mem Sep 1010) chromatography as a 60% 1-propanol- and 1 M NaCl-eluted fraction. Unlike the reference Escherichia coli LPS, QM-1M did not demonstrate any ability to induce cytokines in a human whole blood culture system in this study, whereas QM-1M induced a few cytokines such as interleukin (IL)-8 and tumor necrosis factor-alpha in human monocytic THP-1 cell and human peripheral mononuclear cell (PBMC) cultures in the absence of serum. Fetal calf and human sera decreased the above cytokine induction by QM-1M in THP-1 and PBMC cultures, whereas sera increased activities of the reference LPS. IL-8 induction in the absence of serum in response to QM-1M was demonstrated to proceed through a CD14-independent pathway unlike the reference LPS.

L9 ANSWER 4 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:48186 BIOSIS
DN PREV199900048186
TI Antibiotic-induced release of ***lipoteichoic*** ***acid*** and peptidoglycan from Staphylococcus aureus: Quantitative measurements and biological reactivities.
AU Van Langevelde, P.; Van Dissel, J. T. (1); Ravensbergen, E.; Appelmelk, B. J.; Schrijver, I. A.; Groeneveld, P. H. P.
CS (1) Dep. Infectious Diseases, Leiden Univ. Med. Cent., P.O. Box 9600, 2300 RC Leiden Netherlands
SO Antimicrobial Agents and Chemotherapy, (***Dec., 1998***) Vol. 42, No. 12, pp. 3073-3078.
ISSN: 0066-4804.
DT Article
LA English
AB Antibiotics with different mechanisms of action may vary with respect to their effects on the release and ***immunostimulatory*** activities of cell wall fragments from gram-positive bacteria. Therefore, after Staphylococcus aureus was cultured for 4 h in the absence of antibiotics (control) and in the presence of beta-lactam antibiotics (imipenem, flucloxacillin, or cefamandole) and protein synthesis-inhibiting antibiotics (erythromycin, clindamycin, or gentamicin), the ***lipoteichoic*** ***acid*** (LTA) and peptidoglycan (PG) levels in the bacterial supernatants were measured. beta-Lactam antibiotics greatly enhanced the release of LTA and PG (4- to 9-fold and 60- to 85-fold, respectively), whereas protein synthesis inhibitors did not affect PG release and even inhibited the release of LTA compared to the amount of LTA released in control cultures. The capacity of beta-lactam supernatants to stimulate the production of tumor necrosis factor alpha and interleukin-10 in human whole blood was significantly higher than that of

protein synthesis inhibitor or control supernatants; the amounts of these cytokines released were directly proportional to the concentrations of PG and LTA in the supernatants. Enzymatic degradation of PG in the supernatants indicated that PG was mainly responsible for the observed biological reactivity.

L9 ANSWER 5 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:512245 BIOSIS
DN PREV199800512245
TI Exposure to bacterial products renders macrophages highly susceptible to T-tropic HIV-1.
AU Moriuchi, Masako; Moriuchi, Hiroyuki (1); Turner, Willie; Fauci, Anthony S.
CS (1) NIH, Build. 10, Room 6A11, Bethesda, MD 20892 USA
SO Journal of Clinical Investigation, (***Oct. 15, 1998***) Vol. 102, No. 8, pp. 1540-1550.
ISSN: 0021-9738.
DT Article
LA English
AB Microbial coinfections variably influence HIV-1 infection through ***immune*** activation or direct interaction of microorganisms with HIV-1 or its target cells. In this study, we investigated whether exposure of macrophages to bacterial products impacts the susceptibility of these cells to HIV-1 of different cellular tropisms. We demonstrate that (1) macrophages exposed to bacterial cell wall components such as lipopolysaccharide (LPS) (Gram-negative rods), ***lipoteichoic*** ***acid*** (Gram-positive cocci), and lipoarabinomannan (Mycobacteria) become highly susceptible to T cell (T)-tropic HIV-1 (which otherwise poorly replicate in macrophages) and variably susceptible to macrophage (M)-tropic HIV-1; (2) LPS-stimulated macrophages secrete a number of soluble factors (i.e., chemokines, interferon, and proinflammatory cytokines) that variably affect HIV infection of macrophages, depending on the virus phenotype in question; and (3) LPS-stimulated macrophages express CCR5 (a major coreceptor for M-tropic HIV-1) at lower levels and CXCR4 (a major coreceptor for T-tropic HIV-1) at higher levels compared with unstimulated macrophages. We hypothesize that a more favorable environment for T-tropic HIV-1 and a less favorable or even unfavorable environment for M-tropic HIV-1 secondary to exposure of macrophages to those bacterial products may accerelate a transition from M- to T-tropic viral phenotype, which is indicative of disease progression.

L9 ANSWER 6 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:481535 BIOSIS
DN PREV199800481535
TI Bacterial DNA as an evolutionary conserved ligand signalling danger of infection to ***immune*** cells.
AU Heeg, K.; Sparwasser, T.; Lipford, G. B.; Haecker, H.; Zimmermann, S.; Wagner, H.
CS Inst. Med. Microbiol. Immunol. Hygiene, Tech. Univ., Trogerstr. 39, 81675 Munich Germany
SO European Journal of Clinical Microbiology & Infectious Diseases, (***July, 1998***) Vol. 17, No. 7, pp. 464-469.
ISSN: 0934-9723.
DT General Review
LA English
AB During infection, the innate limb of the ***immune*** system senses danger (pathogens) via constitutively expressed pattern-recognition receptors, and responds with activation and secretion of pro-inflammatory cytokines. Cell-wall components of gram-positive and gram-negative bacteria, such as peptidoglycan, endotoxin or ***lipoteichoic*** ***acid*** , activate via CD14, a prototypic pattern-recognition receptor for carbohydrates. This review article focuses on an alternative recognition system of the innate ***immune*** system for the recognition of bacterial DNA. Bacterial DNA differs from eukaryotic DNA in its frequency of the dinucleotides CG and its lack of methylation. These structural differences appear to be sensed by cells of the innate ***immune*** system such as antigen-presenting cells. As a consequence bacterial DNA serves as an alternate ligand to signal danger of infection. Bacterial DNA and (synthetic) oligonucleotides (ODN) derived thereof are as efficient as endotoxin in activating macrophages and dendritic cells and in triggering release of pro-inflammatory cytokines. In mice sensitized with D-galactosamine (D-GalN), high doses of bacterial DNA from either gram-positive or gram-negative pathogens induce a lethal cytokine syndrome (lethal shock). Therefore, bacterial DNA may represent a hitherto unrecognized pathophysiological entity in host-parasite interactions. Moreover, recent evidence suggests that bacterial DNA or ***immunostimulating*** ODN triggers the ***immunostimulation*** of antigen-presenting cells, and can be utilized as ***adjuvant*** to enhance ***immune*** responses of the adaptive ***immune*** system towards poorly ***immunogenic*** antigens. In fact, foreign DNA might be useful as ***immunotherapeutically*** active ***adjuvant*** to direct adaptive ***immune*** responses towards Th1-dominated ***immune*** reactions. If these findings are operative in humans, ***immunostimulating*** ODN might be used to influence Th2-dominated diseases such as allergy.

L9 ANSWER 7 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:416701 BIOSIS
DN PREV199800416701
TI IL-8 secretion by lung epithelial cells infected with group B streptococci.
AU Goodrum, K. J. (1)
CS (1) Ohio Univ., Athens, OH USA
SO Abstracts of the General Meeting of the American Society for Microbiology, (1998) Vol. 98, pp. 247.
Meeting Info.: 98th General Meeting of the American Society for Microbiology Atlanta, Georgia, USA May 17-21, 1998 American Society for Microbiology
. ISSN: 1060-2011.
DT Conference
LA English

L9 ANSWER 8 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:405837 BIOSIS
DN PREV199800405837
TI Mechanism of gram-positive shock: Identification of peptidoglycan and ***lipoteichoic*** ***acid*** moieties essential in the induction of nitric oxide synthase, shock, and multiple organ failure.
AU Kengatharan, Ken M.; Kimpe, Sjef De; Robson, Caroline; Foster, Simon J.; Thiemermann, Christoph (1)
CS (1) William Harvey Res. Inst., St. Bartholomew's and Royal London Sch. Med. Dent., Charterhouse Square, London EC1M 6BQ UK
SO Journal of Experimental Medicine, (***July 20, 1998***) Vol. 188, No. 2, pp. 305-315.
ISSN: 0022-1007.
DT Article
LA English
AB The incidence of septic shock caused by gram-positive bacteria has risen markedly in the last few years. It is largely unclear how gram-positive bacteria (which do not contain endotoxin) cause shock and multiple organ failure. We have discovered recently that two cell wall fragments of the pathogenic gram-positive bacterium Staphylococcus aureus, ***lipoteichoic*** ***acid*** (LTA) and peptidoglycan (PepG), synergize to cause the induction of nitric oxide (NO) formation, shock, and organ injury in the rat. We report here that a specific fragment of PepG, N-acetylglucosamine-beta-(1fwdarw4)-N-acetylmuramyl-L-alanine-D-isoglutamine, is the moiety within the PepG polymer responsible for the synergism with LTA (or the cytokine interferon -Y) to induce NO formation in the murine macrophage cell line J774.2. However, this moiety is also present in the PepG of the nonpathogenic bacterium Bacillus subtilis. We have discovered subsequently that S. aureus LTA synergizes with PepG from either bacterium to cause enhanced NO formation, shock, and organ injury in the rat, whereas the LTA from B. subtilis does not synergize with PepG of either bacterium. Thus, we propose that the structure of LTA determines the ability of a particular bacterium to cause shock and multiple organ failure (pathogenicity), while PepG acts to amplify any response induced by LTA.

L9 ANSWER 9 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:364102 BIOSIS
DN PREV199800364102
TI Enzyme ***immunoassay*** detecting teichoic and lipoteichoic acids versus cerebrospinal fluid culture and latex agglutination for diagnosis of Streptococcus pneumoniae meningitis.
AU Stuertz, Kristin; Merx, Imke; Eiffert, Helmut; Schmutzhard, Erich; Mader, Michael; Nau, Roland (1)
CS (1) Dep. Neurol., Univ. Goettingen, Robert-Koch-Str. 40, D-37075 Goettingen Germany
SO Journal of Clinical Microbiology, (***Aug., 1998***) Vol. 36, No. 8, pp. 2346-2348.
ISSN: 0095-1137.
DT Article
LA English
AB A newly developed enzyme ***immunoassay*** (EIA) was used to detect the presence of pneumococcal teichoic and lipoteichoic acids in cerebrospinal fluid (CSF) from patients with Streptococcus pneumoniae meningitis who were being treated with antibiotics. All initial CSF samples, which on culture grew S. pneumoniae, were positive in the EIA. A total of 14 subsequent culture-negative samples gave clear signals in the EIA up to day 15 after the onset of antibiotic treatment. For 11 CSF specimens, culture, microscopy, and latex agglutination were negative while the EIA detected pneumococcal antigens. The EIA did not react either with CSF of patients with meningitis caused by bacteria other than S. pneumoniae or by viral pathogens. In conclusion, this EIA can be a valuable tool for the diagnosis of S. pneumoniae meningitis from CSF samples in cases in which prior antimicrobial therapy minimizes the usefulness of culture or other antigen detection tests.

L9 ANSWER 10 OF 596 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1998:304888 BIOSIS
DN PREV199800304888
TI Lipopolysaccharide-related stimuli induce expression of the secretory leukocyte protease inhibitor, a macrophage-derived lipopolysaccharide inhibitor.
AU Jin, Fenyu; Nathan, Carl F.; Radzioch, Danuta; Ding, Aihao (1)
CS (1) Beatrice and Samuel A. Seaver Lab., Dep. Med., Cornell Univ. Med. Coll., New York, NY 10021 USA
SO Infection and Immunity, (***June, 1998***) Vol. 66, No. 6, pp. 2447-2452.
ISSN: 0019-9567.

DT Article
LA English
AB Mouse secretory leukocyte protease inhibitor (SLPI) was recently characterized as a lipopolysaccharide (LPS)-induced product of macrophages that antagonizes their LPS-induced activation of NF-kappaB and production of NO and tumor necrosis factor (TNF) (F. Y. Jin, C. Nathan, D. Radzioch, and A. Ding, Cell 88:417-426, 1997). To better understand the role of SLPI in innate ***immune*** and inflammatory responses, we examined the kinetics of SLPI expression in response to LPS, LPS-induced cytokines, and LPS-mimetic compounds. SLPI mRNA was detectable in macrophages by Northern
blot analysis within 30 min of exposure to LPS but levels peaked only at 24 to 36 h and remained elevated at 72 h. Despite the slowly mounting and prolonged response, early expression of SLPI mRNA was cycloheximide resistant. Two LPS-induced proteins-interleukin-10 (IL-10) and IL-6-also induced SLPI, while TNF and IL-1beta did not. The slow attainment of maximal induction of SLPI by LPS in vitro was mimicked by infection with Pseudomonas aeruginosa in vivo, where SLPI expression in the lung peaked at 3 days. Two LPS-mimetic molecules-taxol from yew bark and ***lipoteichoic*** ***acid*** (LTA) from gram-positive bacterial cell walls-also induced SLPI. Transfection of macrophages with SLPI inhibited their LTA-induced NO production. An anti-inflammatory role for macrophage-derived SLPI seems likely based on SLPI's slowly mounting production in response to constituents of gram-negative and gram-positive bacteria, its induction both as a direct response to LPS and as a response to anti-inflammatory cytokines induced by LPS, and its ability to suppress the production of proinflammatory products by macrophages stimulated with constituents of both gram-positive and gram-negative bacteria.

=> d his

(FILE 'HOME' ENTERED AT 16:21:18 ON 06 JAN 2003)

FILE 'BIOSIS, EMBASE, CAPLUS' ENTERED AT 16:21:34 ON 06 JAN 2003
L1 42 S (PEPTIDOGLYCAN OR MACROPHAGE ACTIVATING LIPOPEPTIDE OR LIPOTE
L2 19 DUP REM L1 (23 DUPLICATES REMOVED)
L3 56 S MALP 2
L4 27 DUP REM L3 (29 DUPLICATES REMOVED)
L5 4 S L4 AND PY<1999
L6 4 DUP REM L5 (0 DUPLICATES REMOVED)
L7 2638 S LIPOTEICHOIC ACID
L8 969 S L7 AND (IMMUN? OR VACCIN? OR ADJUVANT?)
L9 596 S L8 AND PY<1999

=> s l9 and (unrespon? or nonrespon? or innate)
L10 16 L9 AND (UNRESPON? OR NONRESPON? OR INNATE)

=> dup rem l10
PROCESSING COMPLETED FOR L10
L11 8 DUP REM L10 (8 DUPLICATES REMOVED)

=> d bib abs 1-
YOU HAVE REQUESTED DATA FROM 8 ANSWERS - CONTINUE? Y/(N):y

L11 ANSWER 1 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 1
AN 1998:304888 BIOSIS
DN PREV199800304888
TI Lipopolysaccharide-related stimuli induce expression of the secretory leukocyte protease inhibitor, a macrophage-derived lipopolysaccharide inhibitor.
AU Jin, Fenyu; Nathan, Carl F.; Radzioch, Danuta; Ding, Aihao (1)
CS (1) Beatrice and Samuel A. Seaver Lab., Dep. Med., Cornell Univ. Med. Coll., New York, NY 10021 USA
SO Infection and Immunity, (***June, 1998***) Vol. 66, No. 6, pp. 2447-2452.
ISSN: 0019-9567.
DT Article
LA English
AB Mouse secretory leukocyte protease inhibitor (SLPI) was recently characterized as a lipopolysaccharide (LPS)-induced product of macrophages that antagonizes their LPS-induced activation of NF-kappaB and production of NO and tumor necrosis factor (TNF) (F. Y. Jin, C. Nathan, D. Radzioch, and A. Ding, Cell 88:417-426, 1997). To better understand the role of SLPI in ***innate*** ***immune*** and inflammatory responses, we examined the kinetics of SLPI expression in response to LPS, LPS-induced cytokines, and LPS-mimetic compounds. SLPI mRNA was detectable in macrophages by Northern blot analysis within 30 min of exposure to LPS but levels peaked only at 24 to 36 h and remained elevated at 72 h. Despite the slowly mounting and prolonged response, early expression of SLPI mRNA was cycloheximide resistant. Two LPS-induced proteins-interleukin-10 (IL-10) and IL-6-also induced SLPI, while TNF and IL-1beta did not. The slow attainment of maximal induction of SLPI by LPS in vitro was mimicked by infection with Pseudomonas aeruginosa in vivo, where SLPI expression in the lung peaked at 3 days. Two LPS-mimetic molecules-taxol from yew bark and ***lipoteichoic*** ***acid*** (LTA) from gram-positive bacterial cell walls-also induced SLPI. Transfection of macrophages with SLPI inhibited their LTA-induced NO production. An anti-inflammatory role for macrophage-derived SLPI seems likely based on SLPI's slowly mounting production in response to constituents of gram-negative and gram-positive bacteria, its induction both as a direct response to LPS and as a response to anti-inflammatory cytokines induced by LPS, and its ability to suppress the production of proinflammatory products by macrophages stimulated with constituents of both gram-positive and gram-negative bacteria.

L11 ANSWER 2 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 1998:481535 BIOSIS
DN PREV199800481535
TI Bacterial DNA as an evolutionary conserved ligand signalling danger of infection to ***immune*** cells.
AU Heeg, K.; Sparwasser, T.; Lipford, G. B.; Haecker, H.; Zimmermann, S.; Wagner, H.
CS Inst. Med. Microbiol. Immunol. Hygiene, Tech. Univ., Trogerstr. 39, 81675 Munich Germany
SO European Journal of Clinical Microbiology & Infectious Diseases, (***July, 1998***) Vol. 17, No. 7, pp. 464-469.
ISSN: 0934-9723.
DT General Review
LA English
AB During infection, the ***innate*** limb of the ***immune*** system senses danger (pathogens) via constitutively expressed pattern-recognition receptors, and responds with activation and secretion of pro-inflammatory cytokines. Cell-wall components of gram-positive and gram-negative bacteria, such as peptidoglycan, endotoxin or ***lipoteichoic*** ***acid*** , activate via CD14, a prototypic pattern-recognition receptor for carbohydrates. This review article focuses on an alternative recognition system of the ***innate*** ***immune*** system for the recognition of bacterial DNA. Bacterial DNA differs from eukaryotic DNA in its frequency of the dinucleotides CG and its lack of methylation. These structural differences appear to be sensed by cells of the ***innate*** ***immune*** system such as antigen-presenting cells. As a consequence bacterial DNA serves as an alternate ligand to signal danger of infection. Bacterial DNA and (synthetic) oligonucleotides (ODN) derived thereof are as efficient as endotoxin in activating macrophages and dendritic cells and in triggering release of pro-inflammatory cytokines. In mice sensitized with D-galactosamine (D-GalN), high doses of bacterial DNA from either gram-positive or gram-negative pathogens induce a lethal cytokine syndrome (lethal shock). Therefore, bacterial DNA may represent a hitherto unrecognized pathophysiological entity in host-parasite interactions. Moreover, recent evidence suggests that bacterial DNA or ***immunostimulating*** ODN triggers the ***immunostimulation*** of antigen-presenting cells, and can be utilized as ***adjuvant*** to enhance ***immune*** responses of the adaptive ***immune*** system towards poorly ***immunogenic*** antigens. In fact, foreign DNA might be useful as ***immunotherapeutically*** active ***adjuvant*** to direct adaptive ***immune*** responses towards Th1-dominated ***immune*** reactions. If these findings are operative in humans, ***immunostimulating*** ODN might be used to influence Th2-dominated diseases such as allergy.

L11 ANSWER 3 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
AN 1999:130202 BIOSIS
DN PREV199900130202
TI Identification of genes involved in ***innate*** responsiveness to bacterial products by differential display.
AU Jin, Fenyu; Nathan, Carl; Ding, Aihao (1)
CS (1) Cornell Univ. Med. Coll., Box 57, 1300 York Ave., Room A-225, New York, NY 10021 USA
SO Methods (Orlando), (***Dec., 1998***) Vol. 16, No. 4, pp. 396-406.
ISSN: 1046-2023.
DT Article
LA English
AB To explore gene regulation by bacterial lipopolysaccharide (LPS), we compared mRNA profiles of macrophage cell lines from two strains of mice congenic for a locus markedly affecting their ability to respond to LPS. Differential display detected four differentially expressed transcripts. One transcript encoded the mouse homolog of human secretory leukocyte protease inhibitor (SLPI), which was expressed by LPS-hyporesponsive macrophage cells (Lpsd) but not by LPS-normoresponsive cells (LpSn). Among five macrophage cell lines, secretion of SLPI was inversely correlated with ability to produce nitric oxide (NO) and tumor necrosis factor alpha in response to LPS. Stable transfection of LPS-responsive macrophages with SLPI suppressed LPS-induced responses. Interferon-gamma (IFN-gamma), which
corrects the defective LPS response in Lpsd macrophages, suppressed the LPS-induced expression of SLPI and restored LPS response to SLPI-overexpressing macrophages. Besides its role as a LPS response inhibitor, mouse SLPI is also a ***lipoteichoic*** ***acid*** response inhibitor. The expression of SLPI was strongly enhanced by interleukin-10 and -6. SLPI may be an important antiinflammatory molecule in host defense against gram-negative and gram-positive bacteria.

L11 ANSWER 4 OF 8 CAPLUS COPYRIGHT 2003 ACS
AN 1997:459862 CAPLUS
DN 127:134372
TI The hyperlipidemia of infection as part of host defense
AU Grunfeld, Carl; Feingold, Kenneth R.
CS Department of Medicine, University of California, San Francisco, San Francisco, CA, 92093, USA
SO Cytokines, Cholera, and the Gut, [Papers from the Joint Meeting of the United States-Japan Cooperative Medical Sciences Program Panels on Malnutrition and Cholera], Kiawah Island, S. C., Nov. 30-Dec. 3, 1995 (

1997), Meeting Date 1995, 35-41. Editor(s): Keusch, Gerald T.; Kawakami, Masanobu. Publisher: IOS Press, Amsterdam, Neth.
CODEN: 64SIAE
DT Conference; General Review
LA English
AB A review with 40 refs. Changes in lipid metab. are tightly linked to the host response to infection. They are induced by low levels of LPS or cytokines. Most crucial steps in lipid metab. are regulated, including increased hepatic de novo fatty acid and cholesterol synthesis, increased lipolysis with reesterification of fatty acids into triglyceride in the liver, decreased lipoprotein lipase activity with decreased triglyceride clearance, increased hepatic HMG CoA reductase, decreased hepatic cholesterol 7.alpha.-hydroxylase, decreased lysolecithin-cholesterol acyl transferase, increased SAA levels, increased apo J levels and decreased cholesterol ester transfer protein. These changes are usually mediated by regulation of mRNA levels. As a result, lipoprotein prodn. is increased and lipoproteins are directed away from their normal metabolic pathways. The changes in lipid metab. are thought to be part of the acute phase response. The purpose of the acute phase response is to enhance destruction of invading organisms and blunt inflammation. We have demonstrated that lipoproteins can scavenge and detoxify bacterial fragments that induce systemic toxicity, such as LPS and ***lipoteichoic*** ***acid*** . Other labs. have shown a role for lipoproteins in host defense against viruses and parasites. As a consequence, it is likely that lipoproteins are part of ***innate*** ***immunity*** .

L11 ANSWER 5 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 3
AN 1996:61060 BIOSIS
DN PREV199698633195
TI Molecules from Staphylococcus aureus that bind CD14 and stimulate ***innate*** ***immune*** responses.
AU Kusunoki, Takashi; Hailman, Eric; Juan, Todd S.-C.; Lichenstein, Henri S.; Wright, Samuel D. (1)
CS (1) Lab. Cellular Physiol. Immunol., Rockefeller Univ., 1230 York Ave., New York, NY 10021-6399 USA
SO Journal of Experimental Medicine, (1995) Vol. 182, No. 6, pp. 1673-1682. ISSN: 0022-1007.
DT Article
LA English
AB Mammals mount a rapid inflammatory response to gram-negative bacteria by recognizing lipopolysaccharide (LPS, endotoxin). LPS binds to CD14, and the resulting LPS-CD14 complex induces synthesis of cytokines and up-regulation of adhesion molecules in a variety of cell types. Gram-positive bacteria provoke a very similar inflammatory response, but the molecules that provoke ***innate*** responses to these bacteria have not been defined. Here we show that protein-free, phenol extracts of Staphylococcus aureus contain a minor component that stimulates adhesion of neutrophils and cytokine production in monocytes and in the astrocytoma cell line, U373. Responses to this component do not absolutely require CD14, but addition of soluble CD14 enhances sensitivity of U373 cells by up to 100-fold, and blocking CD14 on monocytes decreases sensitivity nearly 1,000-fold. Deletion of residues 57-64 of CD14, which are required for responses to LPS, also eliminates CD14-dependent responses to S. aureus molecules. The stimulatory component of S. aureus binds CD14 and blocks binding of radioactive LPS. Unlike LPS, the activity of S. aureus molecules was neither enhanced by LPS binding protein nor inhibited by bactericidal/permeability increasing protein. The active factor in extracts of S. aureus is also structurally and functionally distinct from the abundant species known as ***lipoteichoic*** ***acid*** (LTA). Cell-stimulating activity fractionates differently from LTA on a reverse-phase column, pure LTA fails to stimulate cells, and LTA antagonizes the action of LPS in assays of IL-6 production. These studies suggest that mammals may use CD14 in ***innate*** responses to both gram-negative and gram-positive bacteria, and that gram-positive bacteria may contain an apparently unique, CD14-binding species that initiates cellular responses.

L11 ANSWER 6 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 4
AN 1995:393928 BIOSIS
DN PREV199598408228
TI Potent stimulation of murine B cells to proliferate and to secrete ***immunoglobulins*** by a ***lipoteichoic*** ***acid*** -like molecule produced by Clostridium botulinum C and D.
AU Campos-Neto, A. (1); Mengel, J. O.; Oliveira-Silva, D. A.; Bonini, P. V.; Taketomi, E.; Stashenko, P. P.
CS (1) Infectious Disease Res. Inst., 1124 Columbia St., Suite 464, Seattle, WA 98104 USA
SO Brazilian Journal of Medical and Biological Research, (1995) Vol. 28, No. 5, pp. 575-584. ISSN: 0100-879X.
DT Article
LA English
AB Bacterial products have served as important ***immunological*** tools to study lymphocyte activation. The lipopolysaccharides of the Gram-negative bacteria are well known to be potent activators of B lymphocytes. Several Gram-positive bacteria produce exotoxins that are superantigens for T cells. In the present study, we demonstrate that the Gram-positive bacteria Clostridium botulinum C and D produce a high molecular weight mitogen (Cb mitogen) that is a potent activator of murine B lymphocytes. The Cb mitogen was discovered as a consequence of our attempt to investigate a possible superantigen activity present in the botulinum exotoxins. We observed initially that mouse spleen cells were strongly stimulated to proliferate by culture supernatants of C. botulinum C and D. However, the characterization of the responding cell ruled out superantigen because only the B lymphocytes were stimulated to proliferate and to secrete ***immunoglobulins*** , and they did so independent of T cell help. In addition, the molecular characterization of the Cb mitogen demonstrated that-the purified botulinum toxin was devoid of mitogenic activity. In contrast, the fractionation of the culture supernatant of C. botulinum C in an FPLC Superose 12 column indicated that the Cb mitogen was present in the void volume of the column (MW gtoreq 300 kDa) which had no toxigenic activity. However, the fractions containing molecules of 150 kDa were highly toxic for mice and had no mitogenic activity. The possibility that LPS was present as a contaminant in the Cb mitogen preparations was excluded because spleen cells from the LPS ***nonresponder*** C3H/HeJ mice responded well to the Cb mitogen, and the antibiotic polymyxin B, which is an inhibitor of LPS, had no effect on the Cb mitogen activity. However, an anti- ***lipoteichoic*** ***acid*** monoclonal antibody (3-1 mAb) inhibited to a great extent the proliferation of spleen cells induced by the Cb mitogen but had no effect on the LPS or concanavalin A stimulation of these cells. Moreover, the Cb mitogen was specifically adsorbed and eluted from a protein G Sepharose column to which the anti- ***lipoteichoic*** ***acid*** 3-1 mAb had been conjugated. These results support the view that ***lipoteichoic*** ***acid*** is a selective B cell mitogen.

L11 ANSWER 7 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 5
AN 1993:320303 BIOSIS
DN PREV199396028653
TI Induction of macrophage-mediated production of tumor necrosis factor alpha by an L-form derived from Staphylococcus aureus.
AU Kuwano, Koichi; Akashi, Akira; Matsu-Ura, Ikuko; Nishimoto, Mitsunobu; Arai, Sumio (1)
CS (1) Dep. Microbiol., Kurume Univ. Sch. Med., 67 Asahi-machi, Kurume 830 Japan
SO Infection and Immunity, (1993) Vol. 61, No. 5, pp. 1700-1706. ISSN: 0019-9567.
DT Article
LA English
AB We investigated the capability of an L-form derived form Staphylococcus aureus to induce tumor necrosis factor alpha (TNF-alpha) production in murine peritoneal macrophages. The activity for TNF-alpha induction was found in the membrane fraction of the L-form but not in the cytoplasmal fraction purified by the sucrose step gradient centrifugation. TNF-alpha mRNA was also detected in macrophages stimulated with L-form membranes. L-form induced TNF-alpha production in macrophages from both lipopolysaccharide-responsive and - ***unresponsive*** mouse strains. Regardless of the presence of polymyxin B, the activity of TNF-alpha induction of L-form was mostly found in the phenol layer, but not in the aqueous layer, both of which were prepared by phenol extraction method. Fractions of L-form membranes representing molecular mass of approximately between 29 and 36 kDa were primarily responsible for inducing the production of TNF-alpha consistently. Moreover, this stimulatory effect was abolished by digestion with Streptomyces griseus protease. In Western blot (***immunoblot***) analysis with anti- ***lipoteichoic*** ***acid*** antibody, two bands (65 and 45 kDa) were observed in the sodium dodecyl sulfate-polyacrylamide gel electrophoresis of the phenol layer, whereas one band (14 kDa) was observed in either the aqueous layer or ***lipoteichoic*** ***acid*** of S. aureus. These results suggest that the component in the membrane of the L-form, distinct from cell wall components such as teichoic acid or lipopolysaccharide, possesses the capability to stimulate TNF-alpha production by macrophages.

L11 ANSWER 8 OF 8 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 6
AN 1987:69253 BIOSIS
DN BA83:37579
TI STREPTOCOCCUS-MUTANS RIBOSOMAL PREPARATIONS PURIFICATION AND PROPERTIES.
AU GREGORY R L
CS DEP. ORAL BIOL., DENTAL RES. CENT., EMORY UNIV. SCH. DENTISTRY, ATLANTA,
GEORGIA 30322, U.S.A.
SO MICROBIOS, (1986) 48 (194), 43-60.
CODEN: MCBIA7. ISSN: 0026-2633.
FS BA; OLD
LA English
AB Ribosomal preparations were obtained from Streptococcus mutans. Sucrose density gradient analysis showed the ribosomes to be 70S and dissociated subunits to be 56S and 34S. The ribosomal preparation contained 57.4% RNA and 42.6% protein and gave an absorption maximum at 260 nm and a minimum at 235 nm and ribosomal particles were approximately 150-180 .times. 190-220 .ANG. as determined by electron microscopy. ***Immunodiffusion*** analysis of pooled antiserum raised by injecting the ribosomal preparation into rabbits disclosed precipitin lines with glucosyltransferase and ***lipoteichoic*** ***acid*** preparations from S. mutans. Gas chromatography showed rhamnose and glucose to be present in the ribosomal preparation indicating the presence of nonribosomal carbohydrate materials. The ribosomes were able to synthesize precipitable polypeptides when exogenous mRNA and tRNA were added and antiribosomal antibodies reduced this activity. Protease treatment rendered the ribosomal preparation less ***immunogenic*** in rats and

less antigenic when the ribosomal preparation was used to coat erythrocytes for passive haemagglutination assays, while RNase treatment of the ribosomal preparation had no effect, suggesting that a protein(s) is the principal ***immunogenic*** moiety of the ribosomal antigen. Polyacrylamide gel electrophoresis of the ribosomal preparation revealed 27 protein bands of which five were found to react with hyperimmune rabbit antisera to the S. mutans ribosomal preparation by Western blot analysis. Washing the ribosomal preparation with 1 M NH4Cl did not remove any of the five ***immunogenic*** ribosomal protein antigens indicating that these were ***innate*** ribosomal proteins.

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	DB=USPT,PGPB,JPAB,DWPI; PLUR=YES; OP=ADJ		
L9	L8 and (unresponsive or nonresponsive)	138	L9
L8	(mouse or mice) same (bacteri$ cell component$ or LPS or endotoxin or peptidoglycan or lopoteichoic acid or mycobacterium tuberculosis)	3023	L8
L7	L6 same (knockout or knock-out or knock out or deficien$ or transgen$)	5	L7
L6	MyD88 or MyD 88	43	L6
L5	L3 same (knockout or knock-out or knock out or deficien$ or transgen$)	3	L5
L4	L2 same (knockout or knock-out or knock out or deficien$ or transgen$)	4	L4
L3	TLR2 or Toll like receptor 2	50	L3
L2	L1 same (knockout or knock-out or knock out or deficien$ or transgen$)	4	L2
L1	TLR4	44	L1

END OF SEARCH HISTORY